THE PROCESSING OF ERRORS AND OTHER SALIENT STIMULI IN ADULTS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

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The processing of errors and other salient stimuli in adults with attention-deficit/hyperactivity disorder

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders characterized by age-inappropriate levels of inattention and/or hyperactivity/impulsivity, which often persists into adulthood and has an important impact on social, academic, or occupational functioning. In this chapter, I first define the concept of ADHD and the main characteristics of the disorder, followed by a description of its etiological factors and the most influential neuropsychological theories developed to explain deficits in ADHD. I then outline the existing evidence on the processing of errors and other salient events in ADHD, which is the central focus of this dissertation. This chapter ends with the formulation of our research objectives and an overview of the chapters included in this dissertation.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

Attention-deficit/hyperactivity disorder (*ADHD*) is an early onset neurodevelopmental disorder, characterized by age-inappropriate levels of inattention and/or hyperactivity/impulsivity. According to the *Diagnostic and Statistical Manual of Mental Disorders* – fifth edition (*DSM-5*, American Psychiatric Association [APA], 2013), several inattentive or hyperactive/impulsive symptoms must be present for at least six months, before the age of 12 and in two or more settings, resulting in impairment in social, academic, or occupational functioning. Furthermore, three presentations are specified: i) predominantly inattentive presentation; (ii) predominantly hyperactive/impulsive presentation, and (iii) combined presentation. Within a given setting, symptom manifestation varies depending on situational factors, such as reward receipt and intensity, supervision, external stimulation, etc. (APA, 2013).

Although there is an age-dependent decline in symptoms (e.g., Biederman, Mick, & Faraone, 2000; Faraone, Biederman, & Mick, 2006), ADHD often persists into adolescence and adulthood, with a significant number of individuals that remain relatively impaired and continue to meet the DSM diagnostic criteria (e.g., Karam et al., 2015; Klein et al., 2012). In addition, symptoms may manifest differently or more subtly in adulthood. For example, the manifestation of hyperactivity often becomes less obvious in adulthood and is frequently expressed as inner restlessness or excessive fidgeting (e.g., Kooij et al., 2010). In comparison to the previous edition of the DSM (*DSM-IV-TR*, APA, 2000), amongst other minor updates, the symptom threshold for adults and adolescents (age 17 and older) was therefore slightly changed in *DSM-5* (APA, 2013), as adolescents and adults are now required to meet less DSM criteria in comparison to children to receive a diagnosis (i.e., at least five instead of six out of nine for inattention and/or hyperactivity/impulsivity).

In addition to the change in symptom threshold from the *DSM-IV-TR* (APA, 2000) to the *DSM-5* (APA, 2013), the classification of ADHD as “a disorder usually first diagnosed in infancy, childhood, or adolescence” was changed to “a neurodevelopmental disorder”, the age of onset criterion was raised from several symptoms present before the age of 7 to the age of 12, and subtypes were replaced by highly equivalent presentation specifiers. Note that all adult participants from the studies in this

dissertation were diagnosed with ADHD based on the criteria of the *DSM-IV-TR* (APA, 2000) and that most instruments used throughout this dissertation were likewise based on these criteria.

ADHD is a very common disorder with a worldwide prevalence rate of 5 – 7% across the life span based on criteria of the *DSM-IV-TR* (APA, 2000; Willcutt, 2012). In children and adolescents specifically, a recent meta-analysis has documented the worldwide prevalence rate of ADHD to be 3.4% (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). For adults, two recent studies assigning diagnosis of ADHD on the basis of *DSM-5* criteria reported a prevalence rate of 3% (Moffitt et al., 2015) and 3.55% (Bernardi et al., 2012). While ADHD is not equally prevalent in both genders in childhood with a male-to-female ratio ranging from 2:1 in general, 1:1 to 3:1 in community samples or 9:1 in clinical samples (APA, 2013; Skounti, Philalithis, & Galanakis, 2007; Willcutt, 2012), it is more gender-balanced in adulthood with a male-to-female ratio of 1.6:1 (APA, 2013; Kessler et al., 2006; Willcutt, 2012).

Comorbidity with other disorders is the rule rather than the exception for ADHD, with more anxiety, mood, learning, tic and autism spectrum disorders in this patient group than in the general population. In childhood specifically, ADHD is highly comorbid with oppositional defiant disorder and conduct disorder. ADHD in adulthood is associated with a range of personality disorders, sleep disorders and substance use disorders (e.g., APA, 2013; Bernardi et al., 2012; Haavik, Halmøy, Lundervold, & Fasmer, 2010; Kooij et al., 2010). Moreover, ADHD is related to poorer functional outcome, such as academic and occupational underachievement, problematic social and family relationships, injuries and accidents, criminality, lower self-esteem, lower physical health, more financial stress and more (self-perceived) stress (e.g., APA, 2013; Bernardi et al., 2012; Dias et al., 2013; Hirvikoski, Lindholm, Nordenström, Nordström, & Lajic, 2009; Kooij et al., 2010; Lackschewitz, Hüther, & Kröner-Herwig, 2008).

Etiology of ADHD

ADHD is clearly a highly complex and heterogeneous disorder as reflected by its many clinical presentations. Although extensively studied, the etiology of ADHD is not yet completely understood. The search for the exact cause of ADHD is furthermore complicated by the complexity and heterogeneity of the disorder at other levels, namely

at the genetic, neurobiological and neuropsychological level. Contributions of genes, environmental factors as well as complex gene-environment interactions and neurobiological factors to the etiology of ADHD have been documented (e.g., Banaschewski, Becker, Scherag, Franke, & Coghill, 2010; Cortese, 2012; Nigg, Nikolas, & Burt, 2010; Thapar, Cooper, Eyre, & Langley, 2013).

Family, twin and adoption studies have consistently provided evidence for a high heritability of ADHD with rates ranging from 60 to 75%. First degree relatives of individuals with ADHD have a two- to eight-fold higher risk for ADHD (Cortese, 2012; Faraone et al., 2005; Nikolas & Burt, 2010; Wood, Buitelaar, Rijsdijk, Asherson, & Kuntsi, 2010). Candidate gene studies have reported a consistent association between ADHD and some genes related to the dopaminergic (e.g., DRD4, DAT1), noradrenergic (e.g., NET1/SLC6A2) and serotonergic (e.g., 5HTT) systems (Banaschewski et al., 2010; Brookes et al., 2006; Cortese, 2012; Thapar et al., 2013). However, no significant genome-wide associations between any of these candidate genes and risk for ADHD have been found, suggestive of a small contribution of individual genes to the overall risk of ADHD. A more recent approach to explain heritability of ADHD focuses on rare genetic variants such as chromosomal duplications and deletions (Ashmore, 2013; Cortese, 2012; Thapar et al., 2013; Williams et al., 2012).

Environmental factors account for 20 to 25% of the etiology of ADHD (Coghill & Banaschewski, 2009; Cortese, 2012). Research has reported associations between ADHD and pre- and perinatal factors (i.e., maternal smoking, maternal alcohol and substance misuse, maternal stress, low birth weight and prematurity), environmental toxins (i.e., pesticides and lead), dietary factors (i.e., nutritional deficiencies or surpluses), and psychosocial adversity (i.e., family adversity and low income). However, none of these factors have a proven causal role in ADHD. Interestingly, the importance of gene-environment interactions in the etiology has been stressed. Genetic and environmental factors interact and probably amplify or dampen one another's expression (Nigg et al., 2010).

In addition to an overall smaller cerebral volume, cortical thinning and delayed cortical maturation, structural neuroimaging studies have also reported abnormalities in fronto-striatal, fronto-temporo-parietal and fronto-cerebellar networks in ADHD (Cortese, 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Hypoactivation in these

latter networks as well as abnormal functional connectivity in some networks (e.g., default-mode network) in ADHD have furthermore been revealed by functional neuroimaging studies (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2015). Furthermore, genetic and neurobiological findings suggest involvement of the dopaminergic and noradrenergic systems in the pathology of ADHD (e.g., Cortese, 2012; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Kooij et al., 2010).

Neuropsychological theories of ADHD

Several theoretical models of ADHD have been developed to explain the underlying mechanisms of ADHD symptoms and the behavioral and cognitive impairments frequently observed in neuropsychological and cognitive research (Johnson, Wiersema, & Kuntsi, 2009). Three very influential and well-investigated models postulate a single core deficit in ADHD. According to the *executive dysfunction theory* (Barkley, 1997), ADHD is explained in terms of a fixed deficit in executive functioning. Executive functions are a collection of higher-order cognitive control processes that enable flexible, goal-directed self-regulatory behavior (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). In particular, abnormal inhibitory control is viewed as the primary deficit in ADHD and is reflected in three processes, namely inhibition of a prepotent response, stopping of an ongoing response, and interference control. According to this model, inhibition is essential for the normal performance of other executive functions (i.e., working memory, self-regulation of affect-motivation-arousal, internalization of speech, reconstitution) and ADHD is associated with secondary impairments in these other executive abilities. Although a few meta-analyses have provided some evidence for executive dysfunction in children and adults with ADHD, these studies point to moderate effect sizes and a lack of universality (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Schoechlin & Engel, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

In line with findings suggesting state-specific and context-dependent performance in ADHD, also in executive function tasks, models have been formulated that have emphasized the dynamic, rather than fixed nature of ADHD, and the role of contextual and state factors in determining the behavioral and cognitive deficits in ADHD (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010). The *delay aversion theory* (Sonuga-Barke, Taylor, Sembi, & Smith, 1992) explains deficits in ADHD in terms of alterations in

motivational mechanisms. A deficit in signaling of future rewards leads to an impulsive drive for immediate reward, reflected behaviorally by a preference for immediate over delayed rewards and less time investment and effort in tedious tasks with the purpose of escaping or avoiding the delay and the negative emotions associated with the delay (Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2004; Sonuga-Barke et al., 2010). Evidence for delay aversion in ADHD has been provided, but it is also neither necessary nor sufficient to cause ADHD (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2008).

The *state regulation deficit theory* (Sergeant, 2005; Sergeant, 2000; van der Meere, 2005) is based on the *cognitive energetic model* of Sanders (1983). The latter theory states that information processing efficiency is determined by elementary cognitive stages, which represent structural processes that mediate between a stimulus and a response (i.e., stimulus encoding, memory search, binary decision and motor preparation), as well as energetic state factors (i.e., arousal, activation and effort). The functioning of the elementary cognitive stages is modulated by both arousal (defined as a time-locked phasic physiological response to input) and activation (referred to as a long-lasting voluntary readiness for action; Pribram & McGuinness, 1975). For optimal task performance, the momentary energetic state of the subject should match the required energetic state. An evaluation mechanism receives feedback on the momentary state from the arousal and activation levels as well as the behavioral response, and is therefore thought to be responsible for self-monitoring and adaptive control. When a suboptimal state is detected, the evaluation mechanism signals the effort system to regulate the arousal and activation levels in order to compensate for this suboptimal state. Crucially, the state regulation deficit theory postulates that neuropsychological deficits in ADHD are due to a non-optimally adjusted energetic (arousal/activation) state as individuals with ADHD have difficulty allocating the necessary additional effort in situations that induce a suboptimal state (Sergeant, 2000; Sonuga-Barke et al., 2010; van der Meere, 2005). Evidence for this theory is derived from studies that have manipulated the presentation rate of stimuli (i.e., event rate), which influences the activation level (Sanders, 1983), and that have shown performance decrements in individuals with ADHD for slow and fast event rates (relative to a moderate event rate; for a meta-analysis, see Metin et al., 2012), as well as from other studies that used psychophysiological indices of effort, such as the P3 (Börger & van der

Meere, 2000; Wiersema, van der Meere, Antrop, & Roeyers, 2006; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006).

No theoretical model focusing on a single core deficit underlying ADHD pathology has proved sufficient to grasp all deficits in ADHD. As it is increasingly being recognized that ADHD is a heterogeneous disorder and its etiology multifactorial, multiple developmental causal pathways to ADHD are now being endorsed in dual or triple pathway theoretical models (Sonuga-Barke, Bitsakou, & Thompson, 2010; Sonuga-Barke, 2003, 2005) that incorporate for example both executive dysfunction (i.e., inhibitory deficits) and delay aversion.

Despite the different emphases of each model, all models have in common that they consider ADHD as a disorder in key aspects of self-regulation, which refers to the effortful or automatized mechanisms that enable behavior to be adapted appropriately to a changing context (Nigg, 2005). Self-regulation is a complex process that comprises the processing of contextual demands, the ongoing monitoring of one's behavior to evaluate whether it is appropriate for a particular context (i.e., self-monitoring), and adjusting behavior when necessary (i.e., adaptive control; Shiels & Hawk, 2010; Shiels, Tamm, & Epstein, 2012). A situation where behavioral adjustments are likely to be necessary is after an error. Behavioral performance of individuals with ADHD is characterized by an increased amount of errors of commission on a variety of tasks (e.g., Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003; Wiersema, Van Der Meere, & Roeyers, 2005), which is differently explained by each model, namely in terms of a general deficit in response inhibition (Barkley, 1997), a different motivational style (Sonuga-Barke et al., 1992) or energetic problems (van der Meere, 2005). Interestingly, a study that manipulated the inhibition load observed that children with ADHD made more errors of commission than typically developing children in both the high load and low load condition, which argues against a response inhibition problem in ADHD but is suggestive of a general error processing problem in ADHD (Van De Voorde, Roeyers, Verté, & Wiersema, 2010). Thus, for appropriate goal-directed behavior on a trial-to-trial basis, processes occurring after error commission should be monitored and adaptive control should be implemented when necessary in order to avoid making an error on the next trial.

ERROR PROCESSING

Support for deficient behavioral adaptive control after errors in ADHD has been provided by studies that show diminished post-error slowing (PES) in ADHD (Balogh & Czobor, 2014; Shiels et al., 2012). PES, first described by Rabbitt (1966), is thought to reflect the slowing down of response time on the trial immediately following an error with the purpose of reducing error probability on the subsequent trial (Balogh & Czobor, 2014; Danielmeier & Ullsperger, 2011). However, deficient adaptive control after errors in ADHD could reflect deficits in processing the error, resulting in a failure to detect the error and in turn precluding adaptive control (Shiels & Hawk, 2010). Error processing, as an important aspect of self-monitoring, could thus provide important insights into the deficient adaptive control and more generally the self-regulatory deficits in ADHD. In this dissertation, I will focus on the processing of errors in adults with ADHD. *Event-related potentials* (*ERPs*) have been used to investigate the processes underlying error processing and these studies have focused on two neurophysiological correlates of error processing, namely the *error-related negativity* and the *error positivity*. Before I elaborate more on the properties and functional meaning of these neural correlates of error processing, I will first describe the ERP technique.

Event-related potentials

ERPs are voltage fluctuations in the ongoing electroencephalogram (EEG) that are time-locked to and brought about by a sensory, motor, or cognitive event, such as the onset of a stimulus or the execution of a manual response (Luck, 2005). EEG is a non-invasive method in which electrical brain activity is measured by electrodes placed on the surface of the scalp. ERPs are extracted from the raw EEG signal, which is larger in amplitude than the ERPs. In order to increase signal-to-noise ratio, ERPs are obtained by averaging across multiple EEG epochs, time-locked to a common event (Rugg & Coles, 1995). This compound neural activity to an event is the result of the sum of the electrical activity generated by certain synchronously activated neuronal populations in different parts of the brain.

Each ERP component has its specific properties and is characterized by its polarity, latency, amplitude and topography (Luck, 2005). The polarity of an ERP component can

either be positive or positive-going or negative or negative-going (i.e., indicated by P or N, respectively), but the polarity is of no particular neurophysiological or functional significance. Its latency gives information on the time course or timing of the underlying processes. ERPs are frequently given a number as an indication of the position of the component in the waveform (e.g., N2 and P3 are a negative and positive component arising around 200 and 300 ms after stimulus onset, respectively) in line with its latency. Its amplitude reflects the degree of engagement of the associated underlying process. Its topography gives information on the distribution of the electrical field across the scalp. In an experimental set-up (e.g., the studies included in this dissertation), ERPs of interest are compared across conditions and/or groups and inferences are made about observed differences in the properties of the ERPs. A difference in ERP amplitude across conditions/groups implies that the process associated with the ERP component is engaged to a different degree, while a difference in ERP latency across conditions/groups suggests that this process is engaged at a different time. A difference in ERP topography across conditions/groups implies different patterns of neural activity (Handy, 2004). In addition, note that some ERPs are given a name that corresponds to the experimental conditions in which they are elicited (e.g., error positivity or novelty P3 as examples from this dissertation).

While ERPs have an excellent temporal resolution in the order of a few milliseconds, in comparison to other neuroimaging techniques such as functional Magnetic Resonance Imaging, they have rather poor spatial resolution because neural activity is recorded from the scalp. Large-density electrode arrays are used to overcome this limitation (i.e., 128 electrodes are used in this dissertation) and this has led to advances in techniques for estimation of the underlying sources giving rise to the ERPs (e.g., standardized low resolution brain electromagnetic tomography or sLORETA) (Pascual-Marqui, 2002). In *Chapter 4* of this dissertation, I will make use of this technique to estimate the underlying neural sources of deficient error awareness in adult ADHD.

A major advantage of ERPs is that they can be used to investigate phenomena that cannot be studied with behavioral methods as they do not require an overt behavioral response. In *Chapter 5* of this dissertation, for example, I make use of this logic as I investigate ERPs to task-irrelevant deviant and novel stimuli (i.e., stimuli that do not require a response). Even in tasks in which an overt behavioral response is given, ERPs

still provide additional information on the processes underlying the behavior (Handy, 2004). In addition, differences in ERPs are sometimes observed in the absence of performance differences, as is also the case in this dissertation, which indicates that valuable covert information provided by the ERPs would otherwise have gone undetected. This is probably because a behavioral measure is the outcome of an internal cognitive process, while an ERP is an electrical correlate of this process (Barry, Johnstone, & Clarke, 2003). I will now focus on the properties and functional significance of the neural correlates of error processing and awareness.

Neural correlates of error processing and awareness

The error-related negativity (ERN) is a fronto-central negative deflection evoked during or immediately after error commission (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) and is taken to reflect a mismatch between the actual and intended or desired action (Coles, Scheffers, & Holroyd, 2001; Falkenstein et al., 1991), post-response conflict (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Carter et al., 1998), or a reward prediction error (Holroyd & Coles, 2002). For correct responses, a similar but smaller negative deflection, namely the correct-related negativity (CRN; Ford, 1999; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000), is elicited and both deflections have the posterior medial frontal cortex (pMFC) as their underlying neural generator (Debener et al., 2005; Dehaene, Posner, & Tucker, 1994). The pMFC is thought to be involved in monitoring situations in which the outcome is worse than expected, and in signaling the need for adjustment (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The general consensus is that the ERN reflects automatic error detection, as it is elicited both after errors that are consciously detected (*aware error*) and errors that remain unnoticed (*unaware error*). However, the idea that the ERN is a pre-conscious correlate of error processing has recently been criticized, as some studies have shown that the ERN can be sensitive to error awareness under specific circumstances (Shalgi & Deouell, 2013; Wessel, 2012).

The ERN is followed by the error positivity (Pe), a large positive wave with a centro-parietal distribution emerging around 300 and 500 ms after error onset, with the pMFC, insula as well as posterior cingulate and more parietal regions as its neural generators (Dhar, Wiersema, & Pourtois, 2011; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter,

2004; Klein et al., 2007; O'Connell et al., 2007). The exact functional significance of the Pe is still debated and several hypotheses have been put forward that suggest that the Pe reflects either the emotional appraisal of the error, a process involved in remedial performance adjustments following errors, a P3b associated with the motivational significance of the error, or the conscious recognition that an error was committed (see for overview Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). The latter hypothesis is widely supported in the literature by ample evidence showing that the Pe is only elicited in case of an aware error, but not after unaware errors or correct responses. Therefore, the Pe is thought to be the neural correlate of error awareness. It is important to note that the Pe sometimes consists of two consecutive and spatiotemporally distinct components and that the above-mentioned Pe refers to the so-called late Pe. Immediately after the ERN, another positive component with a fronto-central distribution is usually elicited which precedes the late Pe. This early Pe is thought to be more functionally similar to the ERN (Debener et al., 2005; Luu, Tucker, & Makeig, 2004; Van Veen & Carter, 2002), although it has been shown that these components have a different topography (Arbel & Donchin, 2009; Endrass, Klawohn, Preuss, & Kathmann, 2012).

Before I turn to evidence on error processing and error awareness in ADHD, the question why some errors are consciously detected and others remain unnoticed first requires an answer. In the following section, I will describe an influential theory on the emergence of error awareness.

The accumulating evidence account

The *accumulating evidence account* (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010) postulates that several sources of information on the error timely become available at different stages and these sources will influence whether an error will remain unaware or will be consciously detected. More specifically, after error commission, a compound internal error evidence signal is build based on several sources of information that progressively become available over time. As the ERN is an early correlate of error processing, it is thought to be influenced by quickly available information, such as the mismatch between the actual and the intended response (Coles et al., 2001) or post-response conflict (Carter et al., 1998). According to the model, error

awareness will arise when the compound internal error signal is strong enough for a threshold of evidence to be surpassed. Therefore, error awareness may be influenced by and emerge from sources of error evidence that become available at later stages after error commission, such as sensory feedback and interoception. The late Pe is argued to be the neural correlate of error awareness and is a late correlate of error processing and it is therefore thought that these later sources of error evidence will mainly influence the late Pe.

Although evidence has been provided that the Pe reflects the accumulated evidence for an error and that this evidence drives the emergence of error awareness (Steinhauser & Yeung, 2010; Steinhauser & Yeung, 2012), no studies have been reported in which the influence of different sources of error evidence on the emergence of error awareness, and more specifically on the late Pe, has been investigated with the purpose of validating the assumptions of the accumulating evidence account (Ullsperger et al., 2010). In this dissertation (*Chapter 2*), I will focus on two later sources of error evidence that are thought to mainly influence the late Pe, namely visual sensory feedback and *interoceptive awareness*. Visual sensory feedback refers to seeing the response finger pressing the response button, while interoception is the perception of autonomic bodily signals and interoceptive awareness refers to the awareness of these signals (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015).

More specifically for interoceptive awareness, it has been shown that only aware errors are accompanied by changes in autonomic activity (Hajcak, McDonald, & Simons, 2003; Wessel, Danielmeier, & Ullsperger, 2011). Moreover, support for a link between the Pe amplitude and a measure of interoceptive awareness has been previously provided, although this study did not make use of an explicit measure of error awareness (see explanation below; Sueyoshi, Sugimoto, Katayama, & Fukushima, 2014). In addition, interoceptive awareness has not only been implicated in error awareness, but in many other cognitive functions that are important for self-regulation, such as emotion processing and regulation (Herbert, Pollatos, & Schandry, 2007) and post-error slowing (Sueyoshi et al., 2014). Support for abnormalities in all these functions in ADHD has been provided (Balogh & Czobor, 2014; Geburek et al., 2013; Herrmann et al., 2009; Shaw, Stringaris, Nigg, & Leibenluft, 2014; Van Cauwenberge, Sonuga-Barke, Hoppenbrouwers, Van Leeuwen, & Wiersema, 2015). Furthermore, the cognitive

energetic model (Sanders, 1983) and state regulation deficit account (van der Meere, 2005) also postulate that monitoring of the bodily state is pivotal for effective state regulation and in extension self-regulation abilities, since these models incorporate feedback loops from the energetic (arousal/activation) state to the evaluation mechanism. The self-regulatory difficulties in ADHD may therefore be related to an inability to become aware of bodily signals. Despite the (hypothesized) importance of interoceptive awareness for the emergence of error awareness and the monitoring of internal state and in extension its possible role in self-regulatory difficulties in ADHD, no studies to date have investigated the ability to become aware of internal autonomic bodily signals in ADHD. In this dissertation (*Chapter 3*), I therefore studied interoceptive awareness by means of a well-validated heartbeat perception task in which participants are instructed to focus on their cardiac activity and count their own heartbeats in separate intervals.

Error processing and awareness in ADHD

ERP studies that mainly focused on the ERN and late Pe have provided inconsistent evidence for deficient error processing and awareness in ADHD. In children with ADHD, findings regarding the ERN are inconsistent as studies reported equally large, smaller as well as larger ERN amplitudes, while the late Pe was more consistently smaller in ADHD (for reviews Johnstone, Barry, & Clarke, 2013; Shiels & Hawk, 2010). In contrast, in adults with ADHD, the ERN was generally smaller while findings for the late Pe are inconsistent (for a meta-analysis: Geburek et al., 2013). Importantly, none but one (discussed below) of these studies used an explicit measure of error awareness in their paradigms as aware errors were not explicitly contrasted to unaware errors. In paradigms truly investigating error awareness (i.e., the paradigm used in this dissertation), participants are asked whether they noticed they had made an error and are instructed to indicate this consciously detected error for example by pressing an extra verification button not related to the main task. By means of this explicit measure of error awareness, (ERPs elicited to) aware errors can be dissociated from (those evoked for) unaware errors (Ullsperger et al., 2010) and this distinction is needed to unequivocally provide evidence for deficient error awareness in ADHD.

The only study in adults with ADHD that made use of an explicit measure of error awareness while also distinguishing between the early and late Pe, reported generally more errors but less consciously detected errors as well as smaller late Pe amplitudes to aware errors in adults with ADHD, which is suggestive of deficient error awareness in ADHD. In addition, the ERN for aware and unaware errors was unaltered in ADHD, while the early Pe was generally smaller in ADHD for both aware and unaware errors as well as for correct responses. Although these findings suggest deficient error awareness in ADHD, more research is clearly needed to replicate these findings. In this dissertation (*Chapter 4*), I therefore studied error awareness in adults with ADHD by means of a paradigm that incorporates an explicit measure of error awareness and tried to uncover the mechanisms underlying deficient error awareness in ADHD.

PROCESSING OF OTHER SALIENT STIMULI

An aware error is a salient event

An (aware) error can be seen as a salient event, because of its infrequent nature, its task-relevance, and because it signals the need for behavioral adjustments. *Salience* is defined as the motivational relevance of a stimulus for the observer determined by bottom-up distinctive properties of the stimulus and/or by top-down processes such as expectations, goals or the mental state of the observer (Cunningham & Brosch, 2012; Uddin, 2014), by some authors referred to as priority instead of salience (Awh, Belopolsky, & Theeuwes, 2012; Fecteau & Munoz, 2006; Ptak, 2012). A stimulus can therefore be salient for several reasons, such as its contextual rareness, its novelty, its behavioral significance in a given context (Zaehle et al., 2013), its emotional valence, etc. Interestingly, it has been shown that the salience network, consisting of the pMFC, anterior insula and orbitofrontal cortex (Seeley et al., 2007), is activated during the processing of all kinds of salient stimuli. This network, with the highly interconnected anterior insula as its central hub, detects the most salient internal or external stimuli and signals other brain regions to generate appropriate behavioral responses to these salient stimuli, and thereby has a critical role in cognition and attention (Menon & Uddin, 2010; Uddin, 2014). This salience network strongly overlaps with the regions activated during error processing (Ullsperger et al., 2010). Crucially, enhanced insula activation was

observed for aware compared to unaware errors (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007) and during the emergence of the Pe (Dhar et al., 2011), which suggests that an aware error is processed as a salient event.

The processing of salient targets and novels

The processing of two types of salient stimuli other than errors is studied by means of an oddball task. In this task, infrequent salient targets and novels are embedded in a stream of frequently presented standard stimuli. Specific variants of the stimulus-locked P3 component are elicited to these salient stimuli, namely the P3b to task-relevant targets and the novelty P3 to task-irrelevant novels. The P3b is a positive deflection between 300 and 600 ms after stimulus onset with a parietal distribution. Its amplitude is associated with working memory context updating (Donchin & Coles, 1988). It reflects the amount of top-down attentional resources allocated to a stimulus (Kok, 2001). In contrast, the novelty P3 is a fronto-central positive peak between 300 and 400 ms after stimulus onset and reflects the bottom-up allocation of attention to distracting task-irrelevant stimuli and is deemed the neural correlate of the orienting response (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007).

Although almost always studied independently, the processing of errors in part resembles the processing of targets as both stimuli are infrequent and behaviorally significant. Likewise, the processing of errors partly resembles the processing of novels because both are infrequent and unexpected. Studies comparing errors and targets on the one hand and errors and novels on the other hand in the same paradigm or across paradigms, have observed activation overlap in the anterior insula for these stimuli (Harsay, Spaan, Wijnen, & Ridderinkhof, 2012; Wessel, Danielmeier, Morton, & Ullsperger, 2012). These comparative studies also found no reliable difference between the topographies of the Pe and the P3b (Leuthold & Sommer, 1999) and observed significant correlations between the Pe amplitude and (the effect of target-to-target interval on) the P3b amplitude (Davies, Segalowitz, Dywan, & Pailing, 2001; Ridderinkhof, Ramautar, & Wijnen, 2009), in line with the hypothesis that the late Pe to aware errors reflects a P3b to the motivational significance of errors (Overbeek et al., 2005). In addition, these studies showed that sources underlying the ERN and Pe

explained significant parts of the novelty P3 (Wessel, Danielmeier, Morton, & Ullsperger, 2012; Wessel, Klein, Ott, & Ullsperger, 2014).

General salience processing deficit in ADHD

In ADHD, structural abnormality of the insula (Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012) as well as altered functional connectivity between the salience network and other networks (Sidlauskaite et al., 2015) has been reported. Other authors claim that the salience network in ADHD is characterized by immaturity (Aboitiz, Ossandón, Zamorano, Palma, & Carrasco, 2014), which is suggestive of a general deficit in processing of salient stimuli in ADHD. Indeed, individuals with ADHD do not only show deficits in the processing of (aware) errors (Balogh & Czobor, 2014; Geburek et al., 2013; Shiels & Hawk, 2010), but also show abnormalities in the processing of a range of salient stimuli, such as rewards (e.g., Luman, Tripp, & Scheres, 2010) and emotional stimuli (e.g., Herrmann et al., 2009). Specifically for targets, a smaller P3b to targets is consistently observed in children (Johnstone et al., 2013) as well as adults with ADHD (Szuromi, Czobor, Komlósi, & Bitter, 2011). In contrast, findings are less consistent for the processing of novels, with larger (Gumenyuk et al., 2005; van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007) or equally large (Jonkman et al., 2000) novelty P3 amplitudes for children with ADHD across different paradigms. Research in adult ADHD is very scarce, but findings suggest deficient novelty processing (Marzinzik et al., 2012). Importantly, the conceptualization of the novel differs greatly across studies, in that the novel can be either associated with meaning or not, be visually simple or complex, be repeated or unique on each occurrence, which complicates making firm conclusions across these studies on novelty processing in ADHD. Findings therefore seem to converge to a general problem of salience processing in ADHD. However, more research is needed to further our understanding of salience processing in ADHD by better delineating different kinds of salient stimuli (*Chapter 5*).

Interestingly, internal bodily signals from the autonomic nervous system are also processed primarily by the anterior insula (Craig, 2009; Craig, 2011). The subjective interpretation of these signals, referred to as interoceptive awareness, has been linked to enhanced activation of the anterior insula (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and is argued to be important for the processing of external stimuli. As

mentioned above, interoceptive awareness has been suggested to be one of the sources of error evidence contributing to the emergence of error awareness in the accumulating evidence account (Ullsperger et al., 2010). Support for its importance for processing of other salient external stimuli has already been provided. For example, interoceptive awareness has been shown to correlate with the P3b to targets (Pollatos, Matthias, & Schandry, 2007).

RESEARCH OBJECTIVES OF THE DISSERTATION

It is not yet clear why some errors remain unaware and other errors are consciously detected. The accumulating evidence account (Ullsperger et al., 2010) has provided a framework to the emergence of error awareness, but the assumptions regarding the sources of error evidence that underlie the emergence of error awareness have not yet been tested. The first aim of this dissertation was to test some of the assumptions of the accumulating evidence account (Ullsperger et al., 2010) in a paradigm that used an explicit measure of error awareness in order to gain more insight into the processes that lead to error awareness.

As the ability to become aware of internal autonomic bodily signals (more specifically heartbeats) has been argue to play a crucial role in error awareness and in monitoring the internal state (state regulation deficit model), the second aim of this dissertation was to examine interoceptive awareness in adult ADHD.

In addition, inconsistent support for deficient error awareness in ADHD has been provided (Geburek et al., 2013; Shiels & Hawk, 2010) and only one study in ADHD so far has implemented an explicit measure of error awareness in their paradigm (O'Connell et al., 2009). The third aim of this study was therefore to further explore error awareness in adult ADHD in a paradigm that used an explicit measure of error awareness.

Moreover, in addition to error processing deficits, individuals with ADHD also show abnormalities in the processing of other salient stimuli, which may suggest a general deficit in salience processing. The fourth aim of the current dissertation was to examine whether individuals with ADHD are characterized by deficient processing of targets and novels.

OVERVIEW OF THE CHAPTERS

This doctoral dissertation consists of six chapters. *Chapter 1* (current chapter) is the general introduction of this dissertation. *Chapter 2* to *5* are empirical chapters, describing the findings of the conducted studies. These empirical chapters are described in more detail below. *Chapter 6* is the general discussion of this dissertation, which comprises an integrated overview of the main findings of this dissertation, theoretical, methodological and clinical implications of the findings, limitations of the conducted studies, and suggestions for future research.

Chapter 2 describes an ERP study in which typically developed adults performed a speeded Go/No-Go task in which they were instructed to press an extra response button when they had consciously detected an error. This explicit measure of error awareness enabled us to contrast aware and unaware errors. The assumption of the accumulating evidence account (Ullsperger et al., 2010) that several sources of error evidence, which timely become available at different stages after error commission, underlie the emergence of error awareness, is tested. I focused on two sources of error evidence, namely visual sensory feedback and interoceptive awareness that are believed to become available at later stages in the post-error onset interval and are thus thought to mainly influence the late Pe. The influence of visual sensory feedback on the emergence of error awareness was investigated by manipulating hand visibility of the response hand in a between-subjects design. Interoceptive awareness is measured by means of a well-validated heartbeat perception task in which participants are instructed to focus on their own cardiac activity and count their own heartbeats within three separate intervals (e.g., Pollatos et al., 2007).

Chapter 3 presents a study in which interoceptive awareness in adult ADHD was investigated. Adults with and without ADHD were compared on an objective (i.e., heartbeat perception task) and subjective (i.e., the awareness subscale of the Body Perception Questionnaire) measure of interoceptive awareness. The importance of examining interoceptive awareness in ADHD is twofold. First, it is one of the sources of error evidence hypothesized to underlie the emergence of error awareness (*Chapter 2*). Second, the ability to become aware of bodily signals is pivotal for monitoring of the current energetic state and thus for effective state regulation.

In *Chapter 4*, the same speeded Go/No-Go task with an explicit measure of error awareness was used. Error awareness in adults with and without ADHD was investigated by comparing ERPs between groups. In addition, a source localization technique (i.e., sLORETA; Pascual-Marqui, 2002) was applied to reveal the underlying neural sources of deficient error awareness in adult ADHD.

Chapter 5 describes an ERP study in which the processing of several kinds of salient stimuli is systematically compared between adults with and without ADHD. Participants performed a four-stimulus oddball task that comprised a frequently presented standard stimulus and three different categories of equally infrequent stimuli: task-relevant targets, task-irrelevant non-targets and task-irrelevant novels. We applied specific contrasts to disentangle the pure effects of deviance (non-targets vs. standards), targetness (targets vs. non-targets) and novelty (non-targets vs. novels; Zaehle et al., 2013).

Important to note is that the empirical chapters in this dissertation are stand-alone manuscripts, which have either been published, have been submitted or are currently under review. It is therefore possible that there is considerable overlap between the chapters.

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CHAPTER 2

JOINTS EFFECTS OF SENSORY FEEDBACK AND INTEROCEPTIVE AWARENESS ON CONSCIOUS ERROR DETECTION: EVIDENCE FROM EVENT-RELATED BRAIN POTENTIALS[1]

ABSTRACT

Error awareness has been argued to depend on sensory feedback and interoceptive awareness (Ullsperger et al., 2010). We recorded EEG while participants performed a speeded Go/No-Go task in which they signaled error commission. Visibility of the effector was manipulated, while interoceptive awareness was measured with a heartbeat perception task. The late Pe was larger for aware than unaware errors. The ERN was also found to be modulated by error awareness, but only when the hand was visible, suggesting that its sensitivity to error awareness depends on the availability of visual sensory feedback. Only when the response hand was visible, the late Pe amplitude to aware errors correlated with interoceptive awareness, suggesting that sensory feedback and IA synergistically contribute to the emergence of error awareness. These findings underscore the idea that several sources of information accumulate in time following action execution in order to enable errors to break through and reach awareness.

[1] Based on Godefroid, E., Pourtois, G. & Wiersema, J. R. (2016). Joint effects of sensory feedback and interoceptive awareness on conscious error detection: Evidence from event related brain potentials. *Biological Psychology, 114,* 49-60. http://doi.org/10.1016/j.biopsycho.2015.12.005

INTRODUCTION

Adaptive goal-directed behavior requires the ability to detect one's own errors in order to make flexible behavioral adjustments. A distinction can be made between errors that remain unnoticed and those that are consciously detected. In paradigms used to investigate error awareness, participants are usually instructed to signal the occurrence of consciously perceived errors by pressing a verification button after the onset of these incorrect actions (e.g., Dhar, Wiersema, & Pourtois, 2011; Modirrousta & Fellows, 2008; Rabbitt, 1968; Rabbitt, 2002; Ullsperger et al., 2010), enabling the contrast between aware and unaware errors. Impaired error awareness has been related to several clinical conditions (Klein, Ullsperger, & Danielmeier, 2013), such as attention-deficit hyperactivity disorder (ADHD; O'Connell et al., 2009; Wiersema, Van Der Meere, & Roeyers, 2009), substance abuse (Hester, Simoes-Franklin, & Garavan, 2007), schizophrenia (Mathalon et al., 2002) and autism spectrum disorder (ASD; Vlamings, Jonkman, Hoeksma, van Engeland, & Kemner, 2008), dementia (Mathalon et al., 2003), or anosognosia (Vocat, Staub, Stroppini, & Vuilleumier, 2010). Thus, the study of error awareness in healthy participants could help gain a better insight into self-regulatory problems characterizing these patient groups.

Early after error commission, a negative fronto-central deflection is observed in the event-related potential (ERP), referred to as the *error-related negativity* (*ERN*; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) or the error negativity (Ne; Falkenstein et al., 1991), which has been source-localized to the posterior medial frontal cortex (pMFC; Debener et al., 2005; Dehaene, Posner, & Tucker, 1994). Noteworthy, the ERN is also elicited after errors that are not consciously detected and often a smaller ERN-like waveform (correct-related negativity: CRN; Ford, 1999; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000) is observed after correct responses, especially when using speeded tasks creating uncertainty regarding accuracy. Furthermore, discrepant findings regarding the modulation of the ERN by error awareness have been reported in the literature, with some studies finding no amplitude difference between aware and unaware errors (Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blow, Band, & Kok, 2001; O'Connell et al., 2007), while others reported larger ERN amplitude for aware compared to unaware

errors (Shalgi & Deouell, 2012; Wessel, Danielmeier, & Ullsperger, 2011; see for review Wessel, 2012).

After error commission, the ERN is followed by a large positive wave, the *error positivity* (*Pe*). This positivity often consists of two consecutive and spatiotemporally distinct subcomponents (Arbel & Donchin, 2009; Endrass, Klawohn, Preuss, & Kathmann, 2012; O'Connell et al., 2009): an early fronto-central component (early Pe) followed by a later centro-parietal deflection emerging around 300-500 ms after error onset (late Pe). Earlier studies have unequivocally established that specifically this latter centro-parietal component is related to error awareness as it is only observed for consciously detected errors (and not for unaware errors). This is in line with earlier notions about the resemblance of the late Pe with the stimulus evoked P3b, which may reflect the emotional appraisal of an error (Dhar et al., 2011; Endrass et al., 2012, 2007; O'Connell et al., 2007; Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; Wessel et al., 2011) or processing of the motivational significance of rare and distinctive or motivationally significant events, such as deviant response errors (Endrass et al., 2012; Overbeek et al., 2005; Ridderinkhof, Ramautar, & Wijnen, 2009).

According to the *accumulating evidence account* (Ullsperger et al., 2010), during an error trial several factors at different stages may influence whether an error will eventually be consciously detected or go unnoticed. More specifically, in the interval spanning from committing to signaling an error, an internal error signal is shaped based on several sources of information that progressively become available over time. The ERN is argued to be influenced by quickly available (motor-related) information, such as the mismatch between the efference copy and the actual response (mismatch hypothesis, Coles, Scheffers, & Holroyd, 2001) or post-response conflict (conflict hypothesis, Carter et al., 1998). In line with this notion, recently, evidence was obtained for a main generator of the ERN in the supplementary motor area, as opposed to the rostral cingulate zone (Bonini et al., 2014). According to this model, error awareness may emerge from sources of error evidence that successively become available at later stages in the post-error onset interval, namely sensory feedback (e.g., proprioceptive, auditory or visual sensory feedback), and interoceptive awareness (IA), with the latter presumably contributing to error awareness at a later stage than sensory feedback. The late Pe, as a neural correlate of error awareness, appears later during an aware error

trial and these latter sources of information (i.e., sensory feedback and IA) are thus thought to mainly influence the Pe amplitude at consecutive stages following error commission, but the early ERN component to a lesser extent though. Yet, to the best of our knowledge, the influence of different sources of error evidence on the Pe as a neural correlate of error awareness has not yet been systematically investigated. The aim of the current study was therefore to explore the possible influence of two of these sources of error evidence, namely sensory feedback and IA, on the (late) Pe component (as well as the preceding ERN).

The first aim of this study was to examine the influence of visual sensory feedback from the button press on the emergence of error awareness by manipulating hand visibility of the response hand in a between-subjects design in order to avoid possible carry-over effects from one condition to the other one. Only visual sensory feedback (i.e., seeing the response finger pressing the response button) was considered and other aspects of sensory feedback, such as auditory feedback (i.e., the sound elicited by the response button) or proprioceptive sensory feedback (i.e., the motion or position of the response finger or effector), were not manipulated and held constant across the two groups. A previously validated speeded Go/No-Go task was used in which participants were asked to signal error awareness by means of a second verification button, while high-density (128 channels) EEG was recorded concurrently (Aarts & Pourtois, 2010; Dhar et al., 2011; Vocat, Pourtois, & Vuilleumier, 2008). According to the dominant model put forward by Ullsperger et al. (2010) and based on the assumption that the Pe amplitude varies according to the strength of the accumulated error evidence (Steinhauser & Yeung, 2012), participants should become less aware of their errors and show smaller Pe amplitudes under conditions of reduced sensory feedback (i.e., when the effector is not visible). We thus expected a smaller Pe amplitude to aware errors in the hand-covered condition compared to the hand-visible condition, which would also be reflected behaviorally in fewer aware errors and/or a slower error-signaling response.

The second goal of our study was to investigate the contribution of IA on error awareness. IA relates to the ability to subjectively interpret bodily signals from the autonomic nervous system that are processed primarily in the (right) anterior insula (Craig, 2011; Craig, 2009), and is postulated to contribute directly to the emergence of the Pe (Ullsperger et al., 2010). Prior research has shown changes in autonomic activity

to be specific for conscious errors. Only errors that reached awareness were accompanied by changes in autonomic activity, such as heart rate deceleration (Danev & Dewinter, 1971; Hajcak, McDonald, & Simons, 2003; Wessel et al., 2011), increase in pupil size (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005), larger skin conductance responses (Hajcak et al., 2003) and increased amygdala activity (Pourtois et al., 2010). Furthermore, both IA (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004) and error awareness have been linked to enhanced activation in the (anterior) insula (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007), which is part of the salience network (Seeley et al., 2007). This network has been argued to support appropriate behavioral responses to motivationally salient events (Menon & Uddin, 2010; Pessoa, 2009) and to play a critical role in the coordination of other large scale brain networks (Uddin, 2014). Using high density EEG combined with a distributed source localization method, Dhar, Wiersema and Pourtois (2011) previously found indirect evidence for insula activation to aware errors during the emergence of the Pe, as hypothesized by Ullsperger and colleagues (2010). These findings furthermore suggest an important role for awareness of bodily responses or signals in the emergence of error awareness. According to the model of Ullsperger et al. (2010), individuals with high IA should be more aware of their (response) errors and hence show larger Pe amplitudes for aware errors than individuals with low IA, a hypothesis that has not been validated at the empirical level yet. In the current study, we therefore sought to evaluate whether error awareness, indexed by the (late) Pe amplitude, is indeed dependent on IA. To this aim, a standard heartbeat perception task was used (Mental Tracking Method; Schandry, 1981) to assess IA. IA has been extensively measured by means of this task in the past, which rates the participants' ability to perceive their own heartbeats consciously (Herbert, Pollatos, & Schandry, 2007; Pollatos, Matthias, & Schandry, 2007) and substantial individual differences have been demonstrated for this ability. Critchley, Wiens, Rotshtein, Ohman, and Dolan (2004) elegantly showed that activity in the right anterior insula predicted accuracy during the heartbeat perception task and that gray matter volume in this brain region correlated with IA as well as subjective ratings of IA. Initial support for the putative link between the Pe amplitude (as measured in a Simon task) and IA (as measured by a heartbeat perception task) has recently been provided by Sueyoshi, Sugimoto, Katayama, and Fukushima (2014). These authors found a robust positive correlation between the Pe amplitude and the heartbeat

perception score. However, importantly, contrary to our study, in the study of Sueyoshi and colleagues (Sueyoshi et al., 2014) awareness of errors was not explicitly measured, since aware errors were not signaled and contrasted with unaware errors. As a matter of fact, the distinction between aware and unaware errors is needed to demonstrate with high confidence the existence of a link between error awareness on the one hand and IA (as well as visual sensory feedback) on the other.

To summarize, the main aim of the current study was to investigate the influence of both visual sensory feedback and IA on the Pe and the emergence of error awareness. First, with regard to the influence of visual sensory feedback, we expected a smaller Pe amplitude to aware errors in the hand-covered condition compared to the hand-visible condition, which would also be reflected behaviorally in fewer aware errors and/or a slower error-signaling response. Second, with regard to the influence of IA, we expected participants with high IA to have more pronounced Pe amplitudes to aware errors than subjects who were less proficient in the heartbeat perception task (correlational analyses). In other words, a positive correlation was expected between scores on the heartbeat perception task and Pe amplitudes.

Importantly, we surmised these individual moderating roles of sensory feedback and IA to be significant for the late centro-parietal Pe specifically, since previous research already identified this mid-latency post-error ERP component to be selectively related to error awareness, as opposed to the preceding ERN for example (Aarts & Pourtois, 2010; Endrass et al., 2012; O'Connell et al., 2007). However, we also evaluated the influence of these factors on the ERN, as some studies have reported ERN modulation by error awareness as well (Shalgi & Deouell, 2012; Wessel et al., 2011; Wessel, 2012). In addition, we explored whether and how both factors were linked to each other during the emergence of error awareness. For example, one could reason that action monitoring and error detection in the hand-covered group may depend more on interoceptive cues than the hand-visible group, due to decreased availability of exteroceptive sensory information. On the other hand, it could be that both factors build on each other towards the emergence of error awareness and that reducing visual sensory feedback (covering the hand) also hampers building up of interoceptive information. However, no directional prediction was formulated regarding the possible joint/synergistic effects of IA and sensory feedback during the emergence of error

awareness since no evidence regarding their mutual influence is currently available in the literature from which specific hypotheses could be derived.

METHOD

Participants

In both groups (hand-visible vs. hand-covered), undergraduate University students participated in exchange of 25 Euro compensation. They all signed an informed consent prior to the start of the experiment. None of the participants had a history of neurological or psychiatric problems. In the hand-visible group, the sample consisted of 28 participants (age: *M*(*SD)* = 23.07 years (*4.13*), four males, three left-handed), while in the hand-covered group, 29 students (age: *M*(*SD)* = 22.97 years (*5.15*), six males, three left-handed) participated. In the hand-visible group, the data of one participant were excluded due to technical problems with the recording of the EEG during the testing session. The data of another participant were excluded because of miscomprehension of task instructions. In the hand-covered group, data of one participant were excluded because of excessive blinks and alpha waves in the EEG signal. To avoid that changing task difficulties alone would confound awareness, we decided to analyze the ERP data from the difficult condition only (see description of the task). Therefore, in the hand-visible group, four additional participants were excluded due to an insufficient number of aware error trials collected for ERP analyses (<6; see Olvet & Hajcak, 2009) in the difficult condition. Results are reported for the remaining 22 participants (age: *M*(*SD*) = 22.64 years (*3.18*), two males, two left-handed). Likewise, due to an insufficient number of aware errors, in the hand-covered group, eight additional participants were excluded. Results are reported for the remaining 20 participants (age: *M*(*SD*) = 21.70 years (*2.43*), five males, one left-handed). Exclusion rate was matched between groups ($\chi^2(1) = 0.68$, $p = .41$). The experiment was approved by the local ethics committee of the Faculty of Psychological and Educational Sciences, Ghent University.

Design and stimuli

The experiments were programmed with E-Prime 2.0 software (http://www.pstnet.com/products/e-prime/) and presented on a 19-inch CRT monitor

with 640x480 screen resolution (60Hz refresh rate). Participants were seated in a sound-attenuated and dimly lit room, sitting approximately 60 cm in front of the computer screen.

Go/No-Go task. Stimuli were colored squares, presented on a black background and subtending 4.7 degrees of visual angle. All stimuli were presented foveally. According to the hue-saturation-value color system, color is defined by three parameters: hue (0-360), saturation (0-100) and value (0-100). To create different tints of color, saturation and value were kept constant (both at 100), while hue was varied systematically. Two different spectra of tints were created: (a) the orange spectrum (0 to 60), with red (0) and yellow (60) as extreme colors, and (b) the purple spectrum (240 to 300) with blue (240) and pink (300) as extreme colors. A pilot study revealed that 6 participants were able to distinguish the tints of these spectra. Participants performed a Go/No-Go task, in which a cue always preceded a target. On 60% of the trials (Go trials), cue and target (Go stimulus) had the same tint, requiring a speeded button press. Possible cue-target pairs in the Go trials were red-red (0), yellow-yellow (60), blue-blue (240) or pink-pink (300). On the other 40% of trials (No-Go trials), cue and target (No-Go stimulus) differed in tint, requiring active inhibition of the prepotent response tendency.

For the No-Go stimulus, two difficulty levels (easy and difficult) were created. Easy and difficult No-Go trials were randomly intermixed. In the easy condition, cue and (No-Go) target stimuli were relatively easy to distinguish from each other. The difference in tints of cue and No-Go stimulus covered 25 points of the spectrum. Possible cue-target pairs were orange (25) – orange (50), orange (35) – orange (10), purple (265) – purple (290) and purple (275) – purple (250). In the difficult condition, the tints of the cue and (No-Go) target stimuli were harder to discriminate from one another, because the difference in tints covered only 10 points along the same spectrum. Possible cue-target pairs were red (0) – orange (10), yellow (60) – orange (50), blue (240) - purple (250) and pink (300) – purple (290). Note that No-Go stimuli were matched across conditions in that all elicited effects after the incorrect response could not be imputed to changes in the physical appearance of the stimuli across conditions.

Participants were instructed to respond as accurately and rapidly as possible when the target (Go) stimulus was physically identical to the cue (i.e., having the same perceived color) by pressing a response button on a response box with the index finger

of their dominant hand, but to withhold responding when they did not match in color (No-Go). Participants were also asked to report explicitly their errors whenever they felt they had violated this simple rule (i.e., push the go button while the stimulus was actually a No-Go). Error commission had to be indicated by pressing a second verification button as soon as possible following its detection (using a separate key of the response box located to the left of the main response button, to which participants had to make a lateral movement with the same response finger). Crucially, response hand visibility was manipulated between groups. In the hand-visible group, participants' response hand was visible during the entire experimental session, while participants in the hand-covered group could not rely on visual sensory feedback from their response hand as a rectangular cardboard box covered their hand fully, starting from the wrist. For both groups, the response hand was positioned at the exact same location. Task instructions emphasized both accuracy and speed. A response limit was set for Go stimuli to induce time pressure and in turn increase error commission. At the start of every block, the initial response limit was set at 350 ms. For every participant individually, the limit was adjusted by means of an algorithm and updated online for every trial. This algorithm has already been used previously extensively (Aarts & Pourtois, 2010; Dhar et al., 2011; Koban, Pourtois, Vocat, & Vuilleumier, 2010; Pourtois et al., 2010). In short, the current RT is compared against the updated RT limit, which corresponds to the average of this RT and the preceding RT. If the participant happens to respond above this limit (slow hit), a negative feedback is presented, while if he happens to respond below this limit (fast hit), no feedback is presented (see below).

Due to the manipulated difficulty of the No-Go trials and the induced time pressure, the task resulted in a sufficient number of aware errors and unaware errors, in addition to hits. Aware errors were defined as responses to No-Go stimuli that were followed by overt reporting (i.e., verification button was pressed). Unaware errors were defined as responses to No-Go stimuli that were not followed by overt detection (i.e., no key press of the verification button was registered). Hits were defined as correct responses to Go stimuli, regardless of their actual speed (fast and slow hits were collapsed; see Aarts, De Houwer, & Pourtois (2013) for a similar approach). Omissions were defined as omitted responses to Go stimuli.

A trial started with a white fixation cross (visual angle of 0.5 degrees) presented for 1500 ms, after which the cue appeared for 500 ms. Before target presentation, a delay was introduced with a random duration between 500 and 1000 ms, precluding its anticipation. The target remained visible until a response was given, with a maximum duration of 1000 ms. After target presentation, the course of the trial depended on the identity of the target (Go or No-Go). When the participant made a fast hit or omitted a response to a Go stimulus, a black screen was shown for 1500 ms. In case of a slow hit, after a delay of 500 ms, a feedback screen indicating that participants were too slow was presented for 500 ms. When participants withheld responding to a No-Go stimulus, the black screen was presented again. In case of an error, they had 1500 ms to press the verification button during which a black screen was presented (see Figure 1).

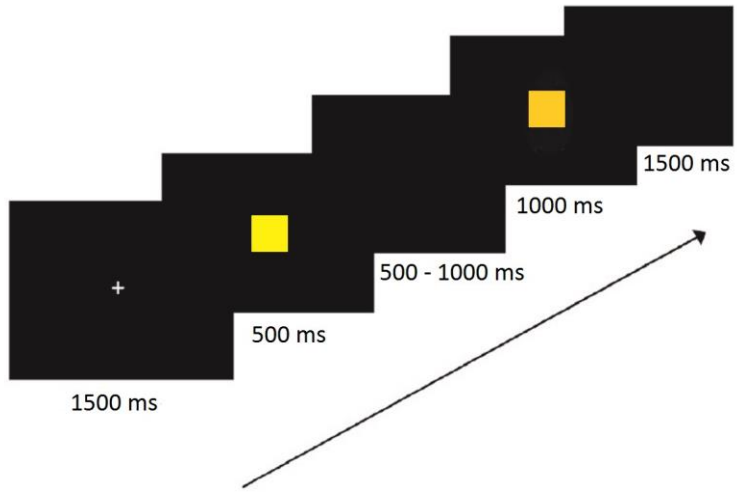

Figure 1. Example of a No-Go trial. After error commission, participants had 1500 ms to indicate (by means of an additional key press) error awareness.

Twelve practice trials were administered at the beginning of the experiment to familiarize the participants with the manipulation of tints and to ensure they understood the instructions properly. In the hand-covered group, participants performed the twelve practice trials without covering of the response hand. The task consisted of 6 blocks, each block containing 36 Go trials and 24 No-Go trials, with a total number of 360 trials (216 Go trials, 72 No-Go trials in the easy condition, 72 No-Go trials in the difficult condition). A short break was introduced between two consecutive blocks. The total duration of the experimental session was about 35 min.

Heartbeat perception task. In both groups, we used the Mental Tracking Method proposed by Schandry (1981), which is widely used to assess IA, is well validated and reliable (Cronbach's alpha: .69-.90) and has a good test-retest reliability (Jones, Collins, Dabkowski, & Jones, 1988). It was administered twice, at the beginning and the end of the testing session. During this task, participants were encouraged to focus on their own cardiac activity and instructed to silently count the number of heartbeats within three separate intervals varying in length. The intervals lasted for 25, 35, and 45 s and the start and end of the interval were indicated by a soft start and stop tone. It was stressed that they were not allowed to take their pulse or use any other bodily cues to facilitate counting. After the stop signal, participants verbally reported the number of counted heartbeats during a resting period of 30 s. Participants were not informed about the length of the intervals and were not given feedback on their performance. A heartbeat perception score was calculated, following standard practice (Herbert et al., 2007; Pollatos, Herbert, Matthias, & Schandry, 2007), according to this formula: $1/3\ \Sigma\ (1 - (|\text{recorded heartbeats} - \text{counted heartbeats}|) / \text{recorded heartbeats})$. Per interval, a difference score of the number of recorded and counted heartbeats was created, which was in turn divided by the number of recorded heartbeats, subtracted from 1, summed and averaged by the number of intervals. This way, the heartbeat perception score could vary between 0 and 1, with high scores indicating small differences between recorded and counted heartbeats and in turn a high IA.

The electrocardiogram was recorded analogous to the electroencephalogram (EEG) through external electrodes attached to the upper and lower left rib cage. R-waves were detected offline via a custom-made R-top algorithm.

EEG acquisition and data reduction

The EEG was continuously recorded at a sampling rate of 1024 Hz with a 128-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands). The signal was referenced online to a CMS-DRL ground. Vertical EEG was recorded from infraorbital and supraorbital electrodes placed in line with the pupil of the right eye, while horizontal EEG was acquired through electrodes positioned on the outer cantus of each eye. Data was recalculated offline against the average reference and down-sampled to 512 Hz sampling rate. A low pass filter of 80 Hz (48 dB/oct), a high pass filter of 0.05 Hz

(48 dB/oct) and a 50 Hz Notch filter were applied. By means of the method of Gratton and colleagues (Gratton, Coles, & Donchin, 1983) the signal was corrected for blinks. ERPs of interest were computed offline with Brain Vision Analyzer 2.0 (Brain Products, GmbH, Munich, Germany). Segmentation was performed relative to response onset with an interval ranging from 200 ms before to 1000 ms after response onset. Each segment was baseline corrected to the entire pre-response onset interval. Artifacts were semi-automatically detected and rejected with a ± 100 µV criterion relative to baseline. Noisy electrodes were interpolated using a spherical spline procedure (order of spline = 4). The amount of noisy electrodes interpolated never exceeded 10% of the total number of electrodes (Keil et al., 2014), with a range of 0 – 12. We computed individual averaged data for correct (hits) and incorrect responses, separately for aware and unaware errors. Finally, a 30 Hz low-pass filter (48 dB/oct) was applied to the individual averaged data. Grand average waveforms were computed separately for the three conditions (hits, aware errors, unaware errors).

Data analysis

Performance. For commission errors, a mixed ANOVA with outcome (2 levels: aware errors and unaware errors) as within-subjects factor and group (2 levels: hand-visible vs. hand-covered) was performed. For the RT data, a mixed ANOVA with outcome (3 levels: hit RT, aware error RT and unaware error RT) as within-subjects factor and group (2 levels: hand-visible vs. hand-covered) was performed. Furthermore, independent samples *t*-tests were used to compare the hand-visible group with the hand-covered group for the other performance measures. As we had clear a priori predictions regarding the verification RT (hand-covered > hand-visible), a one-tailed *t*-test was used.

Electrophysiological measures. In accord with previous studies investigating error awareness (Dhar, Wiersema, & Pourtois, 2011; O'Connell et al., 2009), an early negative deflection (ERN) was clearly generated at FCz for all three conditions, while, as expected, a late Pe was elicited specifically for aware errors at more posterior leads along the midline, including CPz. Thus, based on the obvious topographical properties of the current data set as well as earlier ERP studies using similar task settings (see Dhar et al.,

2011), the mean amplitudes of the ERN and late Pe were calculated, respectively, between 0 and 100 ms at FCz, and 300-500 ms at CPz following error commission.

First, to compare our ERP results with findings from previous studies investigating error awareness and to test the influence of hand visibility on error awareness, we performed a mixed ANOVA with the within-subjects factor outcome (3 levels: hits, aware errors and unaware errors) and the between-subjects factor group (2 levels: hand-visible and hand-covered) separately for the ERN amplitude at FCz and the late Pe amplitude at CPz. When sphericity assumptions were violated as indicated by a Mauchly test, Greenhouse-Geisser corrections were used. Amplitude values of the ERN and Pe for aware errors vs. unaware errors, aware errors vs. hits, and unaware errors vs. hits were submitted to a priori planned and orthogonal contrasts with Bonferroni corrections. If a group by outcome interaction was apparent, a paired samples *t*-test was applied per group comparing activity to aware versus unaware errors, in line with our specific research question, concerning the modulation of the Pe (and ERN) by error awareness. In addition, independent samples *t*-tests on the difference scores between outcomes (aware errors minus unaware errors, aware errors minus hits, unaware errors minus hits) were performed.

Visual inspection of the ERP data suggested a modulation of the ERN by error awareness at more posterior sites (Cz and CPz), dependent upon the availability of sensory feedback (see Figure 2), In the hand-visible condition, a conspicuous ERN to aware errors but not to unaware errors was observed at Cz and CPz. In contrast, in the hand-covered condition, no such modulation of the ERN by error awareness was seen. Instead, error awareness seemed to emerge later in time, as an enhancement of the Pe amplitude was observed in the hand-covered compared to the hand-visible group. Based on these important observations, an additional mixed ANOVA was performed with outcome (3 levels: hits, aware errors and unaware errors) and electrode (Cz, CPz) as within-subjects factors and group (2 levels: hand-visible and hand-covered) as a between-subjects factor for ERN. When sphericity assumptions were violated as indicated by a Mauchly test, Greenhouse-Geisser corrections were used. Bonferroni corrected *t*-tests were applied. Again, if a group by outcome interaction was apparent, a paired samples *t*-test was applied per group comparing activity to aware versus unaware

errors. Figure 2 shows the grand average waveforms at FCz, Cz and CPz, for hits, aware errors, and unaware errors, separately for the hand-visible and hand-covered group.

Correlations. Correlational analyses were performed between IA on the one hand and the behavioral or neurophysiological correlates of error awareness on the other hand to shed light on the role of IA in the emergence of error awareness. As we had clear a priori predictions about the direction of these correlations (see Introduction section), one-tailed *p*-values were reported.

RESULTS

Behavioral data

Behavioral data are reported in Table 1, separately for the two groups. For commission errors, a significant main effect of outcome was revealed ($F(1, 40) = 100.61$, $p < .001$, $\eta^2_p = .72$). Both groups had significantly more unaware errors than aware errors ($p < .001$). The interaction between outcome and group was not significant ($F(1, 40) = 0.23$, $p = .64$, $\eta^2_p = .01$).

Outcome also showed a main effect for RT ($F(2, 80) = 20.67$, $p < .001$, $\eta^2_p = .34$). For both groups, a longer RT for unaware errors than for hits ($p < .001$) or aware errors was evidenced ($p < .001$). A marginally significant RT difference between hits and aware errors was observed ($p = .08$). The interaction between outcome and group did not reach significance ($F(2, 80) = 0.46$, $p = .63$, $\eta^2_p = .01$).

Furthermore, a marginally significant group difference was found for omissions ($t(40) = 1.91$, $p = .06$, $d = 0.60$), bearing in mind that very few omissions were made (see Table 1). Importantly, in line with one of our predictions, the between-group comparison of the median verification RT yielded a significant difference ($t(40) = -1.72$, $p = .05$, one-tailed, $d = 0.53$), with a delay in the error signaling response in the hand-covered group compared to the hand-visible group.

Table 1. Behavioral data for the hand-visible and hand-covered group

	Hand-visible group	Hand-covered group
Hit RT	288 (24)	289 (19)
Number of aware errors	13.7 (4.6)	14.4 (7.1)
Number of unaware errors	39.9 (13.4)	43.2 (13.2)
Omissions	9.8 (17.1)	2.5 (2.6)
Aware error RT	282 (35)	278 (20)
Unaware error RT	304 (43)	307 (32)
Verification median RT	571 (121)	643 (147)

Note. Values are shown as means (*SD*).

Electrophysiological measures

With regard to the ERN at FCz, the main effect of outcome ($F(2, 80) = 0.44$, $p = .52$, $\eta^2_p = .01$), the main effect of group ($F(1, 40) = 0.55$, $p = .47$, $\eta^2_p = .01$), and the interaction between outcome and group did not reach significance ($F(2, 80) = 0.03$, $p = .97$, $\eta^2_p < .01$).

For the late Pe at CPz, a significant main effect of outcome was found ($F(2, 80) = 19.16$, $p < .001$, $\eta^2_p = .32$). The amplitude of the late Pe was significantly larger for aware errors than for hits ($p = .001$) or unaware errors ($p < .001$). The main effect of group did not reach significance ($F(1, 40) = 0.00$, $p = .99$, $\eta^2_p < .001$), but a significant interaction between group and outcome ($F(2, 80) = 3.36$, $p < .04$, $\eta^2_p = .08$) was found. Follow-up paired *t*-tests showed a significant difference for Pe amplitudes for aware versus unaware errors in the hand-covered group ($p < .001$, $d = 1.05$) as well as in the hand-visible group ($p = .016$, $d = 0.56$). Further, in the hand-visible condition, no difference was found between the late Pe to hits and aware errors ($p = .22$, $d = 0.28$), while the late Pe for hits was larger than for unaware errors ($p = .02$, $d = 0.58$). In the hand-covered condition, the amplitude of the late Pe to aware errors was larger than for hits ($p = .001$, $d = 0.96$), while no difference was found for the late Pe between hits and unaware errors ($p = .16$, $d = 0.33$). In addition, an independent samples *t*-test performed on the difference scores between aware and unaware errors indicated a marginally significant group difference ($t(40) = -1.69$, $p = 0.09$, $d = 0.52$). Moreover, the aware errors-hits difference was marginally significant between the two groups ($t(40) = -2.02$, $p = 0.05$, $d = 0.62$), while the unaware errors-hits difference was not ($t(40) = -1.11$, $p = 0.27$, $d = 0.34$).

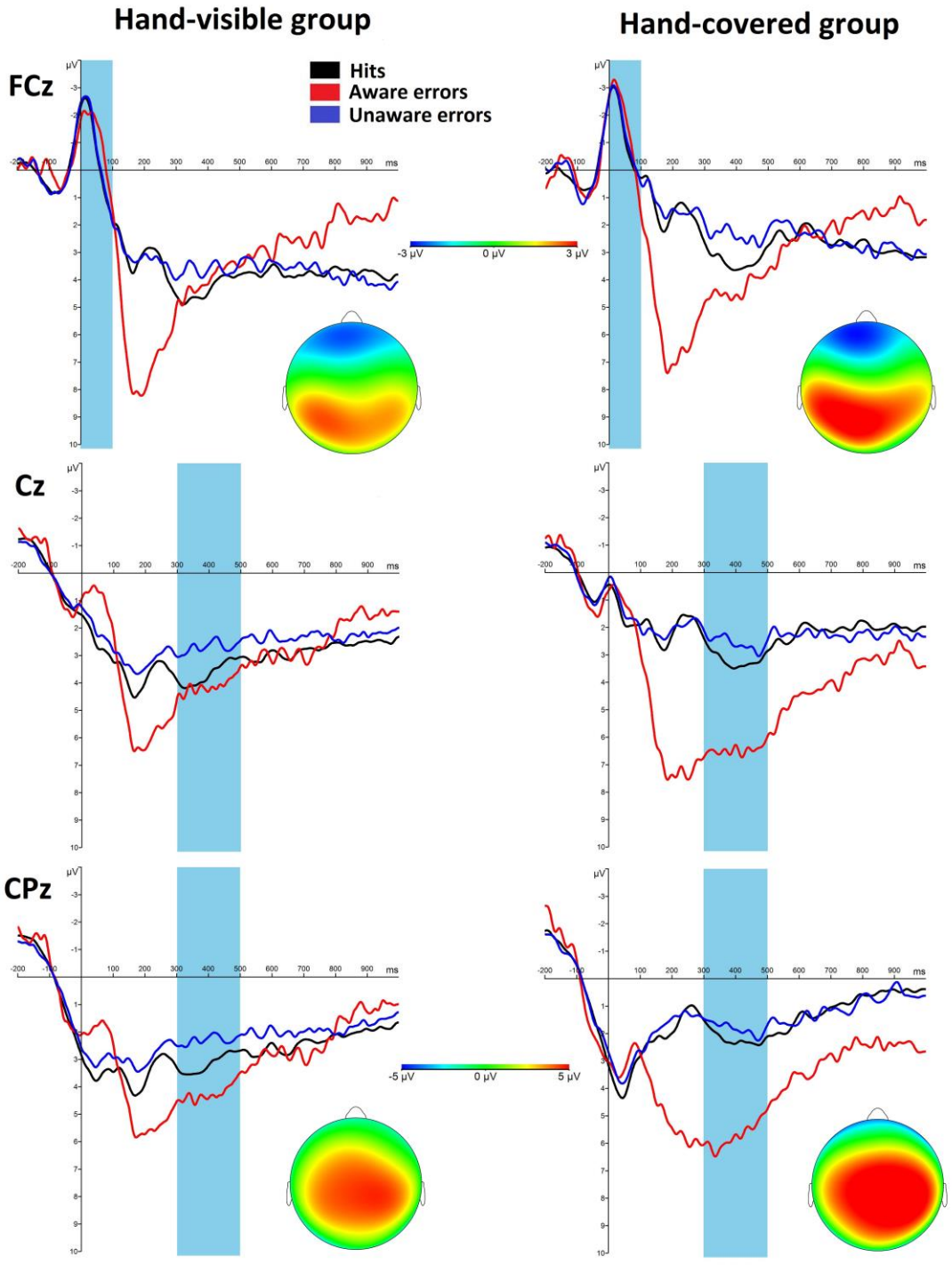

Figure 2. Grand average waveform at FCz, Cz and CPz for hits, aware errors and unaware errors, separately for the hand-visible and hand-covered group. The topographical maps (horizontal view) correspond to the time windows of the ERN for aware errors (0-100 ms) and the Pe for aware errors (300-500 ms).

The seemingly stronger error awareness effect at the Pe level in the hand-covered compared to the hand-visible group condition may be explained when considering the pattern of results found for the ERN at the electrodes Cz and CPz. Visual inspection of the ERP data (see Figure 2) suggests a modulation of the ERN at more posterior sites by error awareness, dependent upon the availability of sensory feedback. In the hand-visible group, a clear ERN to aware errors but not to unaware errors was apparent, compared to the hand-covered group, in which a small negativity of equal size was elicited to aware errors, unaware errors and hits. In the hand-visible group a smaller Pe amplitude was evidenced, while a more pronounced Pe to aware errors was noticed in the hand-covered group, which suggests that error awareness seemed to emerge later in time in the latter condition (see Figure 2).

We therefore performed an additional mixed ANOVA with outcome and electrode (Cz, CPz) as within subject factors and group as between-subjects factor, to better understand this dependency on availability of sensory feedback of the ERN modulation by error awareness (at these specific centro-parietal electrode sites along the midline). A main effect of outcome was found ($F(2, 80) = 6.86$, $p = .01$, $\eta^2_p = .15$). The amplitude of the ERN for aware and unaware errors was significantly larger than the corresponding CRN elicited for hits (respectively $p = .01$, $p = .01$), while no significant difference was found between aware and unaware errors ($p = .22$). The interaction between group and outcome, however, showed a trend-significant effect ($F(2, 80) = 2.38$, $p = .10$, $\eta^2_p = .06$). As none of the interactions with electrode were found to be significant, values of Cz and CPz were collapsed in the follow-up analyses. These analyses revealed that in the hand-visible group, the ERN to aware errors was significantly larger than to unaware errors ($p = .04$, $d = 0.46$), while this was not the case in the hand-covered group ($p = .76$, $d = 0.07$). Further, in the hand-visible condition, the amplitude of the ERN to aware errors was larger than for hits ($p = .01$, $d = 0.68$). The ERN amplitude to unaware errors was larger than the corresponding CRN elicited for hits ($p = .01$, $d = 0.66$). In the hand-covered condition, no significant difference was found between the CRN to hits and the ERN to aware errors ($p = 0.25$, $d = 0.26$), while a marginally significant difference was found between the CRN to hits and the ERN to unaware errors ($p = .07$, $d = 0.45$). Hence, the findings suggest that the ERN was modulated by error awareness, but only in the hand-visible condition.

Interoceptive awareness and error awareness

Performance on heartbeat perception task. For both groups, the heartbeat perception score acquired at the beginning of the session (hand-visible: *M*(*SD*) = .57 (*.17*), hand-covered: *M*(*SD*) = .69 (*.20*)) correlated significantly with the heartbeat perception score obtained at the end (hand-visible: *M*(*SD*) = .72 (*.16*), $r = .69$, $p < .001$; hand-covered: *M*(*SD*) = .71 (*.21*), $r = .86$, $p < .001$), indicating that the estimate of IA was reliable. Moreover, mean heartbeat perception scores obtained in this study were comparable to previous studies (Herbert et al., 2007; Pollatos et al., 2007). For the hand-visible group, the mean heartbeat perception score was .65 (*SD* = .15; range: .46 - .96), while it was .70 (*SD* = .20; range: .34 - .94) in the hand-covered group. The between-group comparison in mean heartbeat perception score yielded no significant results ($t(40) = -1.05$, $p = .29$, $d = -0.28$).

Correlations: interoceptive awareness and awareness RT. Correlational analyses between the number of aware errors and median verification RT, and the mean heartbeat perception score were performed. The correlation between the mean heartbeat perception score and the number of aware errors did not reach significance, in none of the two groups (hand-visible group: $r = -.29$, $p = .099$, hand-covered group: $r = .16$, $p = .26$). Visual inspection by means of a scatter plot showed that an outlier distorted the marginally significant correlation between the mean heartbeat perception score and the number of aware errors in the hand-visible group. After removal of this outlier, the correlation was no longer trend-significant ($r = -.13$, $p = .28$). In the hand-covered group, a significant negative correlation was observed between the median verification RT and the mean heartbeat perception score ($r = -.42$, $p = .03$), while no such correlation was evident in the hand-visible group ($r = -.02$, $p = .46$). However, a Fisher *z* test revealed that the difference between both correlation coefficients was not significant ($p = .21$, two-sided).

Correlations: interoceptive awareness and the late Pe. To explore at what moment in time following response onset IA could be related to the emergence of error awareness, the mean amplitude of the late Pe to aware errors was broken down into two consecutive bins of 100 ms (bin 1: 300 – 400 ms, bin 2: 400 – 500 ms after error commission) and these time bins were correlated with the mean heartbeat perception

score. In the hand-visible group, at time bin 2 (400 – 500 ms), the Pe amplitude at CPz was significantly positively correlated with the mean heartbeat perception score (r = .45, p = .037; Figure 3), but this was not observed in the hand-covered group (r = -.21, p = .19). A Fisher z test showed that these correlations differed significantly (p = .04, two-sided). Moreover, this association was found to be specific for the late Pe, as the correlation between IA and the ERN to aware errors at FCz, Cz and CPz was not significant (hand-visible: all r's < |.18|, all p's >.42; hand-covered: all r's < |.35|, all p's > .13). These findings demonstrate that, as expected, participants who had higher IA showed larger Pe amplitudes to aware errors than participants with lower IA, with the strongest effect appearing between 400 and 500 ms after error commission. However, surprisingly, this effect was only observed when sensory feedback from the response hand was available, suggesting a possible interaction effect between sensory feedback and IA during the emergence of error awareness.

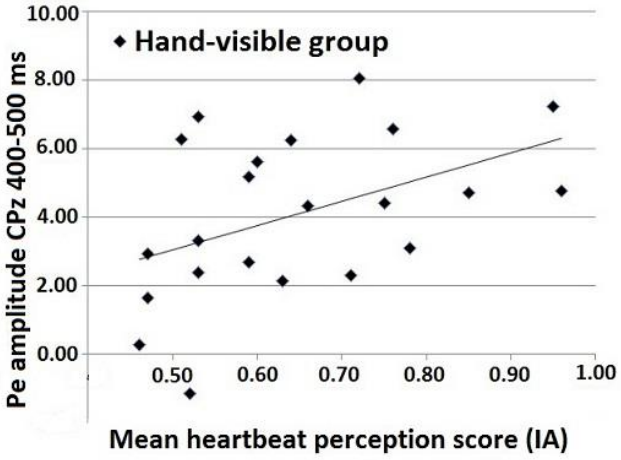

Figure 3. Scatter plot depicting the correlation across subjects between mean heartbeat perception score (IA) and mean Pe amplitude to aware errors at CPz (bin 400-500 ms), for the hand-visible group only.

DISCUSSION

The goal of the current study was to assess whether visual sensory feedback from the response hand and IA might each contribute to foster error awareness. To this end, high-density EEG was recorded while participants performed a speeded Go/Nogo task in which they signaled error commission by means of an extra button press, following standard practice. Hand visibility of the response hand was manipulated between subjects. IA was assessed by means of a standard heartbeat perception task (Herbert et al., 2007; Pollatos et al., 2007). At FCz, the CRN (hits) and ERN (response errors) were equally large, an observation that was compatible with previous studies using speeded paradigms similar to the one used in this study (Dhar et al., 2011; Vocat et al., 2008). The speeded nature of the task and in particular the use of a stringent response deadline (Aarts & Pourtois, 2010; Aarts, Vanderhasselt, Otte, Baeken, & Pourtois, 2013; Dhar & Pourtois, 2011) probably caused participants to be relatively impulsive and hence uncertain about their action at the time of their onset, a factor which has been shown to enhance the CRN amplitude (Pailing & Segalowitz, 2004). In line with many earlier findings in the psychophysiology literature (Dhar et al., 2011; Endrass et al., 2007; O'Connell et al., 2007; Shalgi, Barkan, & Deouell, 2009), we found that the Pe was clearly related to error awareness, being larger for aware errors than for unaware errors. Contrary to our predictions, we found a trend-significantly larger awareness effect (aware minus unaware errors) for the late Pe amplitude when sensory feedback from the response hand was not available. However, this finding seemed to be related to the observation that when visual sensory feedback was available, error awareness may have modulated the preceding ERN component, while only the Pe was modulated by error awareness when the hand was not seen, suggesting that error awareness likely emerged later in time in this condition, as reflected by an enhanced Pe amplitude (and delayed error signaling RT). These Pe results should however be carefully interpreted, as the effect for the Pe was only trend-significant. In addition, caution is needed regarding the interpretation of the ERN results (because error awareness was found to influence the early response-locked ERP signal at central, as opposed to more fronto-central sites, like FCz or Fz where this component usually reaches its maximum amplitude, as observed here as well). Nevertheless, the findings suggest that the sensitivity of the ERN component to error awareness (at least at Cz and CPz) may actually depend upon the

availability of sensory feedback from the response hand, as the ERN modulation by error awareness was only seen when the hand was visible (see also here below in the discussion). Furthermore, supporting our second hypothesis, the Pe amplitude to aware errors was found to be related to the extent of IA. Participants with higher IA showed larger Pe amplitudes to aware errors than participants who were less accurate at the heartbeat perception task. Crucially, this was only observed when visual sensory feedback from the response hand was available to the participants, which dovetails with the assumption that both sources of information interact dynamically during the emergence of error awareness.

The effect of sensory feedback on error awareness

In line with the accumulating evidence account (Ullsperger et al., 2010), the Pe amplitude seemed to be influenced by the availability of visual sensory feedback from the response hand. However, contrary to our predictions, the awareness effect tended to be larger when the response hand was not visible. This may be explained by a systematic modulation of the preceding ERN component by error awareness, dependent on the availability of sensory feedback. When the information from the response hand was available, the ERN (at Cz) was modulated by error awareness. In case of reduced availability of visual sensory feedback, the ERN was not sensitive to error awareness and may have caused error awareness to emerge later in time, which in turn increased the Pe amplitude to aware errors. This result therefore confirms that error awareness may stem from a complex accumulation of evidence process, whereby the lack of an important source of information (regarding error awareness) influences the speed with which this process eventually emerges following action execution. This finding also implies therefore that participants likely needed more time to become aware of their errors, when an otherwise important source of information regarding error commission was omitted, as indirectly confirmed by the verification RT results. Although it remains unclear how this accumulation of evidence precisely operates following error onset to yield the conscious detection of these behaviorally relevant events, our ERP study is among the first to hint at a possible mechanism underlying this utmost important mental process. Here we showed that becoming aware of errors may actually be dependent upon visual sensory feedback from the response hand, in interaction with IA

processes, suggesting that these two sources of information did contribute to brain mechanisms responsible for the conscious detection of response errors.

The finding that the ERN was found to be larger for aware errors, but only when visual sensory feedback from the response hand was available, indicates that ERN modulation by error awareness may depend upon this factor. ERN elicitation was influenced by a source of error evidence (namely visual sensory feedback) available only later in time, thus contradicting Ullsperger's model (2010) that posited that the ERN component is only influenced by quickly available sources of error evidence (e.g., mismatch between the efference copy and the actual response, Coles et al., 2001; or post-response conflict, Carter et al., 1998). The ERN modulation by error awareness in the hand-visible condition was however noticed at more posterior sites (Cz and CPz) than where the ERN typically reaches its maximum amplitude (FCz or Fz). This finding may suggest that early action monitoring at the level of the ERN (with a main pMFC source) would be immune to error awareness (even though this interpretation is currently debated in the literature), while error awareness would be accompanied by the activation of another, partly overlapping component, expressed more posteriorly (Cz), which could be compatible with the involvement of additional posterior cingulate regions, besides the pMFC (Agam et al., 2011; Charles, Van Opstal, Marti, & Dehaene, 2013; Wittfoth, Küstermann, Fahle, & Herrmann, 2008).

The observation that ERN amplitude modulations by error awareness partly depend on the availability of visual sensory feedback is valuable because it may help reconcile in part inconsistent findings reported in the literature regarding the sensitivity (or the lack thereof) of this early response-locked ERP component to error awareness (Dhar et al., 2011; Maier, Steinhauser, & Hubner, 2008; Nieuwenhuis, Aston-Jones, & Cohen, 2005; Wessel, 2012). Our results suggest that these inconsistencies may not only stem from methodological differences in assessing (at the subjective level) error awareness (Shalgi & Deouell, 2012), but they could also very well be imputed to systematic variations across these earlier ERP studies concerning the availability or amount of visual sensory feedback at the time of action execution. Indirect support of an influence of sensory feedback on the ERN amplitude may come from a few studies comparing processing of self-generated errors with errors that were not self-generated (observed errors). Van Schie, Mars, Coles, and Bekkering (2004) compared self-generated errors with

observation of errors made by others and found an ERN for both types of errors, but the ERN was reduced and delayed for observed errors. In a study by Gentsch, Ullsperger, and Ullsperger (2009), it was found that only self-generated errors evoked an ERN, while errors caused by technical malfunction elicited an FRN, which is a negative deflection consistently observed after feedback when outcomes are worse than expected (Holroyd & Coles, 2002).

The effect of interoceptive awareness on error awareness

In line with our predictions, we also observed a significant negative correlation between verification RT and heartbeat detection scores, suggesting faster errors detection for those with better IA. It has to be noted though that this correlation was only significant when the response hand was not visible. However, a Fisher *z* test showed that these two correlations were not statistically different from each other (hand-visible condition vs. hand-covered condition), casting doubt on the condition-specificity of this relationship. Future studies including larger samples might help to resolve this issue.

More straightforward was the relationship between the late Pe (for aware errors, selectively) and IA in the hand-visible condition. A positive correlation was found between the Pe amplitude and the mean heartbeat perception score at the centro-parietal electrode CPz at approximately 400 ms following error commission. This result is in line with the recent findings from Sueyoshi and colleagues (2014) who reported a positive correlation between the Pe amplitude and the heartbeat perception score. However, in our study, we took error awareness into account (while these authors did not in their study), enabling us to unequivocally establish a link between the Pe amplitude, error awareness, and IA. This association was found to be specific for the late Pe, as the ERN to aware errors was not found to correlate with IA in our study. Sueyoshi and colleagues (2014) previously found an association between the ERN amplitude and the heartbeat perception score, but only when faces expressing disgust were presented and not when neutral faces or objects were presented. According to these authors, disgust faces probably evoked a physiological reaction, causing ERN amplitude and IA to be associated, which led them to assume a flexible and situation-specific link between error monitoring and physiological monitoring. By comparison, no emotional stimuli

were presented in our task. The fact that the late Pe correlated with IA in our study fits the assumption of Ullsperger's model (Ullsperger et al., 2010) that sources of error evidence that become available at late stages after error commission, namely IA, may have an influence on late correlates of error detection, namely the late Pe, as opposed to the earlier ERN for example. More generally, our new findings accord with the notion that only the later centro-parietal P300-like component (which shares many similarities with the late Pe) is affected by arousal, is sensitive to salience, reflects awareness and may capture affective or motivational effects related to it (Endrass et al., 2007; O'Connell et al., 2007). In agreement with this interpretation, several theories previously advocated (e.g., Koban & Pourtois, 2014; somatic marker hypothesis, Bechara, Damasio, & Damasio, 2000; accumulating evidence account, Ullsperger et al., 2010) that IA plays a key role in the (conscious) processing of motivationally significant events, which is supported by research on emotion processing (Herbert, Herbert, & Pollatos, 2011; Herbert et al., 2007; Pollatos et al., 2007), and more recently, in relation to decision-making. For example, only for participants who were proficient in the heartbeat perception task was neural activity in the right anterior insula associated with better performance in the Iowa Gamblink task (Werner et al., 2013). Our study adds to this growing literature by showing a unique link between IA and a well-validated electrophysiological correlate of error awareness (Pe), suggesting that the extent to which human participants become aware of their response errors depends, at least in part, on how well they are usually able to consciously perceive autonomic bodily signals.

Interaction between sensory feedback and interoceptive awareness

The fact that no (positive) correlation was observed between the late Pe (for aware errors) and IA in the hand-covered condition suggests that IA supports the emergence of error awareness only when sensory feedback from the response hand is available. In other words, error awareness (late Pe effect) depends on interoceptive information that presumably builds on or adds to the information provided by visual sensory feedback concurrently. Nonetheless, both factors do not seem to work fully independently from each other towards the emergence of error awareness. Our findings rather hint at a weakening of the contribution of interoceptive information to this process when visual sensory feedback is removed. As such, our new findings inform about the complex interaction effect at stake between exteroceptive sensory feedback and IA during the

conscious detection of response errors. Earlier studies focusing on bodily awareness already provided indirect support for an interaction effect between exteroceptive and interoceptive signals (Ainley, Tajadura-Jiménez, Fotopoulou, & Tsakiris, 2012; Suzuki, Garfinkel, Critchley, & Seth, 2013), which are integrated online by the anterior insula (Craig, 2007; Dhar et al., 2011; Simmons et al., 2013). Nonetheless, more research is needed to explore the possible boundaries of this synergistic effect during error awareness.

Clinical implications

The finding that both sensory feedback and IA support the emergence of error awareness not only stresses the importance of better considering their modulatory roles during action monitoring from a methodological or theoretical point of view, but it may also help better understand abnormal action monitoring processes arising in specific psychopathologies that are characterized by deficiencies in error awareness, including ADHD (O'Connell et al., 2009; Wiersema et al., 2009) drug addiction (Hester et al., 2007), schizophrenia (Mathalon et al., 2002), anxiety (Aarts & Pourtois, 2010), depression (Aarts et al., 2013), ASD (Vlamings et al., 2008), dementia (Mathalon et al., 2003), anosognosia (Vocat et al., 2010), and traumatic brain injury (TBI; Hester et al., 2012). In some cases, these impairments might stem from noisy interoceptive or sensory feedback information that in turn blur or delay the conscious detection of response errors. By disentangling the specific contributions of these two important sources of information during error awareness, our findings may contribute to a better understanding of impaired action monitoring and error awareness accompanying these different disorders, which may eventually help optimize treatment options for them.

Limitations

Several limitations have to be mentioned. First, the use of an extra error-signaling response to titrate error awareness has been criticized previously, because it likely entails additional cognitive and attentional processes besides error awareness (for a thorough discussion of this issue, see Ullsperger et al., 2010). However, this standard procedure has been used extensively in many studies previously in the literature and it provides consistent ERP findings (i.e., selective modulation of the Pe component as a

function or error awareness). Second, contrary to our predictions, the reduced availability of sensory feedback from the response hand had no influence on the number of aware errors signaled by the participants. This lack of group difference could be imputed to the use of a stringent response limit/deadline adjusted to the performance of the participant, that probably reduced inter-individual variability and caused all participants to make a relatively balanced amount of unwanted response errors. Third, the between-subjects manipulation of response hand visibility does not allow to fully disentangle the specific contribution of each separate factor (sensory feedback and IA) to the emergence of error awareness. To overcome this problem, future studies should implement a fully orthogonal design and perform regression analyses to uncover the relative contribution of each factor. Fourth, it cannot be excluded that manipulating hand visibility may have caused participants to press the response hand with reduced (or alternatively enhanced) force in the hand-covered condition or to pay less attention to the hand and that this has led to decreased processing of proprioceptive information instead of hand visibility itself. Accordingly, future research is needed to clarify whether visual sensory feedback (in combination with IA) influences error awareness directly, or instead indirectly via some changes in proprioceptive inputs. The observation that a typical ERN can be elicited following errors in a completely deafferented patient (Allain, Hasbroucq, Burle, Grapperon, & Vidal, 2004) suggests however that proprioceptive information does not contribute directly to early error detection. Fifth, this study was confined to clarify effects of visual sensory feedback and interoception on error awareness and other potentially important factors, such as auditory sensory feedback, were therefore not considered in the present case. Further research is warranted to examine the influence of other unexplored sources of error evidence, such as auditory sensory feedback, on the emergence of error awareness.

Conclusion

The present study sought to test the prediction that sensory feedback and IA each supports the emergence of error awareness. Replicating earlier studies (Dhar et al., 2011; Endrass et al., 2007; O'Connell et al., 2007; Shalgi et al., 2009), we found that the late Pe was related to error awareness. Contrary to our predictions, the awareness effect of the Pe amplitude tended to be larger when visual sensory feedback from the response hand was not available (versus when it was). This effect may be explained by

an earlier modulation of the response-locked ERP signal by error awareness (at the level of the ERN), which depends on the availability of visual sensory feedback. Our findings lend support to the second hypothesis by showing that participants who were more interoceptive aware (as measured using an independent and standard heartbeat perception task) had in turn larger Pe amplitudes to errors inadvertently committed during a (separate) speeded Go/No-Go task that were eventually overtly detected. Crucially, this correlation was only observed when sensory feedback from the response hand was available, which confirms that sensory feedback and IA interact dynamically during the emergence of error awareness, as previously put forward in the literature (Ullsperger et al., 2010). As such, this study adds to the growing literature showing that action monitoring and (conscious) error detection do not simply involve motor or premotor control processes in the human brain, but also include a component related to the conscious processing of bodily signals. Finally, these new findings may also fuel research on neurological or psychiatric disorders characterized by impaired error awareness, including ADHD or addiction.

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CHAPTER 3

INTEROCEPTIVE AWARENESS IN ADHD[1]

ABSTRACT

According to the state regulation deficit account, ADHD is related to difficulty applying the necessary additional effort in order to compensate for a non-optimal energetic state (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010). A prerequisite for effective state regulation is the ability to monitor the momentary state. Surprisingly, the question whether the ability to monitor the current state is disrupted in ADHD, has not yet been answered. An organism receives information regarding its bodily state via interoceptive channels, with interoceptive awareness referring to the awareness of these bodily signals, which has been shown to play a crucial role in many cognitive functions (Craig, 2009). This is the first study investigating interoceptive awareness in adults with ADHD. They performed equally well as controls on both objective (heartbeat perception task) and subjective measures (questionnaire) of interoceptive awareness. Findings suggest a preserved monitoring of bodily state in adult ADHD.

[1] Based on Godefroid, E., & Wiersema, J. R. (under review). Interoceptive awareness in Attention Deficit Hyperactivity Disorder. *Research in Developmental Disabilities.*

INTRODUCTION

Attention-deficit/hyperactivity disorder (*ADHD*; American Psychiatric Association [APA], 2013) is a common neurodevelopmental disorder characterized by symptoms of inattention, and/or hyperactivity and impulsivity, which often persists into adulthood (Kooij et al., 2005; Matte et al., 2015). ADHD leads to impairments in social and cognitive functioning in an array of settings. Several etiological models have been introduced in the literature and although they all have their own focus, they have in common that they consider ADHD as a disorder in core aspects of self-regulation (Nigg, 2005; Sergeant, 2000; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006). Researchers have failed to find a fixed core deficit and more recently, the dynamic, rather than the fixed, nature of ADHD and especially the role of contextual and state factors in determining cognitive and performance deficits, has been emphasized (Sonuga-Barke et al., 2010).

The *state regulation deficit account* (*SRD*; Sergeant, 2000; Sonuga-Barke et al., 2010; van der Meere, 2005), which is based on the *cognitive energetic model* (*CEM*; Sanders, 1983, see Figure 1), explicitly stresses the dynamic nature and context-dependency of performance deficits and symptoms in ADHD, and relates it to a non-optimally adjusted energetic (arousal/activation) state. The main idea of the model is that information processing and task performance are dependent on the current energetic state of the organism. More specifically, to perform a task optimally, the current energetic state should match the required (target) energetic state. When there is a discrepancy between the current state and the target state, as scanned by an evaluation system, additional effort should be allocated in order to reduce the mismatch between the current and required energetic state and to counteract a performance decrement. The SRD account states that individuals with ADHD have difficulty allocating the necessary additional effort in situations that induce a non-optimal state (Sergeant, 2000; Sonuga-Barke et al., 2010; van der Meere, 2005).

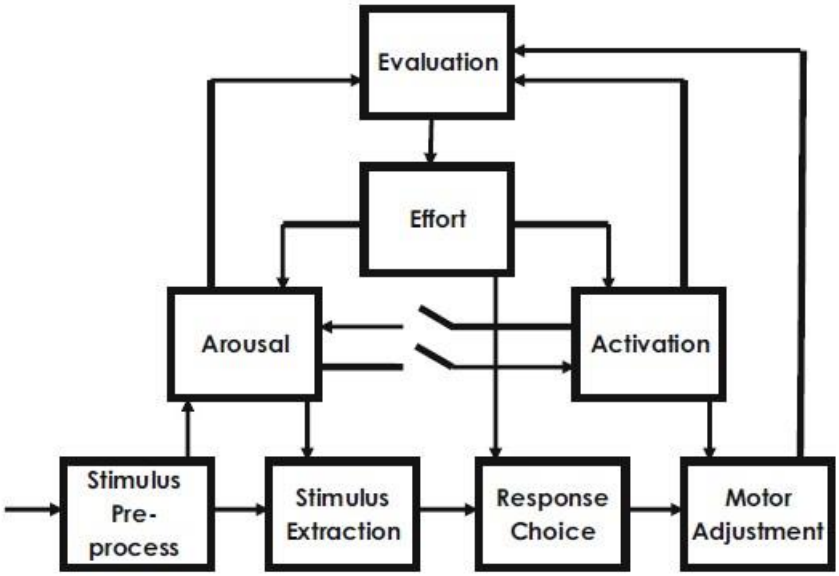

Figure 1. The cognitive energetic model of Sanders (1983).

There is now ample evidence coming from research applying different methodologies showing that individuals with ADHD do not sufficiently allocate the required extra effort to meet task demands (Metin, Roeyers, Wiersema, van der Meere, & Sonuga-Barke, 2012; Wiersema, van der Meere, Van Coster et al., 2006). Studies that have manipulated the event rate (presentation rate of stimuli), which influences the activation level (Sanders, 1983), have shown that ADHD performance is particularly sensitive of such a manipulation and that individuals with ADHD have difficulty to adjust their under-activated (induced by a slow event rate) and over-activated state (fast event rate), resulting in performance decrements (for a meta-analysis, see Metin et al., 2012). Research applying psychophysiological indices of effort, have provided further support for decreased effort allocation in ADHD during conditions that induced a non-optimal state. Specifically during a slow event rate condition (relative to a moderate condition), children with ADHD showed greater mid-band heart rate variability in comparison to typically developing children, indicating less effort allocation in children with ADHD (Börger & van der Meere, 2000). Event-related potential (ERP) research has shown that slower responding in children with ADHD in a slow paced condition was accompanied by a reduced parietal P3 amplitude (they showed a typical P3 in the faster condition), again indicating less effort allocation in non-optimal situations (Wiersema, van der Meere, Van Coster et al., 2006). The same pattern of results was found in adults with ADHD

(Wiersema, van der Meere, Antrop et al., 2006). A recent fMRI study showed that during slow and fast event rates, relative to a moderate event rate condition, the attenuation of default mode network activity as seen in typically developed adults, was lacking in adults with ADHD (Metin et al., 2015). Together these studies have provided convincing evidence for a difficulty in children and adults with ADHD in adjusting the energetic state necessary to counteract a performance decrement during non-optimal conditions. However, it is still not fully understood why this is the case. For example, it is debated whether this really reflects an inability to allocate additional effort or whether it is associated with a general altered motivational attitude (Luman, Tripp, & Scheres, 2010). Further research is warranted to identify the locus in the SRD model that gives rise to the state regulation deficit and self-regulatory difficulties in ADHD.

According to the SRD and CEM models, a prerequisite for effective state regulation is state monitoring: the evaluation systems checks for discrepancies between the current state and the required (target) state and in case of a discrepancy, extra effort is allocated to restore equilibrium. As can be seen in Figure 1, the CEM includes feedback loops from the energetic pools (arousal and activation) to the evaluation system. Hence, a vital prerequisite for effective effort allocation is knowledge of the current state. If the ability to monitor bodily states and to become aware of these signals is impaired, logically, state regulation will be disrupted as well. Surprisingly, there are no studies available that have attempted to address the important question whether ADHD indeed is associated with difficulties in monitoring the current bodily state.

An organism receives information regarding its bodily state via interoceptive channels. Interoception is the perception of autonomic bodily signals, with interoceptive awareness (IA) referring to the awareness of these signals (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015). The anterior insula, as the proposed locus of bodily awareness (Craig, 2009), is heavily involved in interoceptive processes (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Khalsa et al., 2009; Terasawa et al., 2013), and importantly, has also been shown to be directly involved in monitoring discrepancies between the momentary state and target state required for optimal task performance (Otto, Zijlstra, & Goebel, 2014; Paulus & Stein, 2006; Singer, Critchley, & Preuschoff, 2009). IA may not only be crucially involved in state regulation, it has also been shown to play a key role in many other cognitive functions, important for self-regulation (Craig,

2009), such as the processing and regulation of emotions (e.g., Herbert et al., 2007; Pollatos, Herbert, et al., 2007), decision-making (Werner et al., 2013), memory (Garfinkel et al., 2013), error awareness (Sueyoshi, Sugimoto, Katayama, & Fukushima, 2014; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010) and post-error adaptation (Sueyoshi et al., 2014). ADHD has been related to deficits in many of these cognitive functions, such as emotion processing and regulation (Herrmann et al., 2009; Shaw, Stringaris, Nigg, & Leibenluft, 2014; Van Cauwenberge, Sonuga-Barke, Hoppenbrouwers, Van Leeuwen, & Wiersema, 2015), error awareness (O'Connell et al., 2009), and post-error slowing (Balogh & Czobor, 2014). In addition, structural and functional insula abnormalities have been reported in ADHD (Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012; Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2015).

Based on theoretical models and empirical findings, it is clear that IA may play a pivotal role in state regulation and adaptive behavior, and hence in ADHD. It is therefore rather surprising that, as of yet, IA has not been investigated in ADHD. In the current study, we therefore measured IA in adults with ADHD by means of objective and subjective indices. IA was objectively measured by means of a well validated heartbeat perception task (e.g., Craig, 2009; Herbert et al., 2007; Pollatos, Kirsch, & Schandry, 2003), in which participants are instructed to silently monitor their own cardiac activity during three separate intervals. Previous research has shown that this task is sensitive to inter-individual differences in IA, and that enhanced activity of the anterior insula during the heartbeat perception task and local gray matter volume in the anterior insula was positively associated with IA (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). In addition to the heartbeat task, a self-report measure, the Body Perception Questionnaire (BPQ; Porges, 1993) was administered, which contains a subscale gauging the overall awareness of several bodily signals.

Recapitulating, there is ample evidence for the SRD account, claiming that ADHD relates to difficulty adjusting the momentary energetic state by applying the necessary additional effort (Börger & van der Meere, 2000; Metin et al., 2012; Wiersema, van der Meere, Antrop et al., 2006; Wiersema, van der Meere, Van Coster et al., 2006). It is however not known whether this may be due to impairment in the ability to monitor the current bodily state. We therefore studied for the first time IA in adults with ADHD, by means of both objective and subjective measures. Based on existing findings on state

regulation difficulties and behavioral adaptation deficits in ADHD, we hypothesized lower IA in adults with ADHD.

METHOD

Participants

Twenty-five adults with ADHD between 19 and 37 years old (12 males) participated in this study. Data of one male participant were excluded because of the use of physical manipulations during the heartbeat perception task (see Heartbeat perception task below). The results of the remaining 24 participants are reported (mean age: *M*(*SD*) = 23.46 (*4.48*), 12 males, one left-handed). The control group consisted of 23 typically developed adults, matched on age, sex and IQ (mean age: *M*(*SD*) = 23.57 (*3.17*), 13 males, four left-handed). Groups did not differ in age ($F(1, 46) = 0.01$, $p = .926$) or sex ($\chi^2(1) = 0.20$, $p = .654$). The difference in IQ between groups was marginally non-significant ($F(1, 46) = 3.99$, $p = .052$).

Individuals with ADHD were recruited through staff members, advertisements, self-support groups for ADHD, and a local database (adults with ADHD who participated in previous research). All adults with ADHD had a formal diagnosis established by a psychiatrist and completed a semi-structured clinical interview to confirm diagnosis (DIVA; Diagnostisch Interview Voor ADHD bij Volwassenen 2.0, Kooij & Francken, 2010). Adults with ADHD using stimulants were asked to interrupt their medication 48 hr prior to participation in the experiment. Control participants were recruited through an online database and advertisements. Exclusion criteria for all participants were an estimated IQ below 80, history of brain-related illness or neurological disorder and a clinical diagnosis of depression or autism spectrum disorder. Control participants were not included in the study if they exhibited four or more symptoms in the attentive or hyperactive/impulsive domain, as evaluated by the Zelfrapportage Vragenlijst voor Aandachtsproblemen en Hyperactiviteit (ZVAH; Kooij et al., 2010), gauging presence of childhood or adulthood ADHD.

Both groups completed an abbreviated version (Meyers, Zellinger, Kockler, Wagner, & Miller, 2013) of the WAIS-IV (Wechsler Adult Intelligence Scale-IV; Wechsler, 2008),

except for the individuals with ADHD who were recruited through the local database since they had already completed the same abbreviated version (Ryan & Ward, 1999) of the WAIS-III (Wechsler, 1997) in a previous study. Not surprisingly, the adult ADHD group scored significantly higher on the DSM oriented ADHD scale than the control group ($F(1, 46) = 42.19$, $p < .001$). In the ADHD group, 15 individuals exceeded the cutoff (less than 46) of the WURS (Wender Utah Rating Scale; Wender, Ward, & Reimherr, 1993), a measure of presence of childhood ADHD, while no control participants exceeded the cutoff. In the ADHD group, according to the ZVAH (Kooij et al., 2010), presence of childhood ADHD was confirmed for 20 participants (cutoff 6; 8 ADHD predominantly inattention, 12 ADHD combined subtype), while ADHD in adulthood was confirmed in 21 participants (cutoff 4; 7 ADHD predominantly inattention, 14 ADHD combined subtype). No difference in substance abuse, as measured with the DSM oriented scale of the ASR (Adult Self-Report; Achenbach & Rescorla, 2003), was observed between groups ($F(1, 46) = 0.25$, $p = .620$). The ADHD group scored significantly higher on the DSM oriented depression scale of the ASR compared to the control group ($F(1, 46) = 12.55$, $p = .001$), but groups did not differ on the anxiety scale ($F(1, 46) = 2.89$, $p = 0.09$).

Several factors that have previously been shown to affect IA and could confound the results were assessed. First, both anxiety and depression have been shown to be (differently) related to IA (anxiety: e.g., Paulus & Stein, 2010; Pollatos, Traut-Mattausch, et al., 2007; depression: e.g., Furman, Waugh, Bhattacharjee, Thompson, & Gotlib, 2013; Harshaw, 2015; Paulus & Stein, 2010; Wiebking et al., 2010). As mentioned, adults with ADHD scored higher on depression symptoms, but no difference in anxiety symptoms was noticed. Second, alexithymia, which reflects difficulty in identifying and describing feelings and characterized by externally oriented thinking (Sifneos, 1996), has been shown to be negatively correlated with IA (Herbert, Herbert, & Pollatos, 2011). Alexithymia was measured with the TAS-20 (Toronto Alexithymia Scale; Bagby, Parker, & Taylor, 1994). The ADHD group scored significantly higher on the TAS-20 in comparison to the control group ($F(1, 46) = 7.93$, $p = .007$).

Measurements of interoceptive awareness

Heartbeat perception task. The Mental Tracking Method (Schandry, 1981), a well-validated task with good psychometric values (Jones, Collins, Dabkowski, & Jones, 1988) and repeatedly used to measure IA (e.g., Garfinkel et al., 2015; Herbert et al., 2007; Pollatos, Matthias, & Schandry, 2007), was chosen as an objective measure of IA. The heartbeat perception task was programmed using E-Prime 2.0 software (http://www.pstnet.com/products/e-prime/) and presented on a 19-inch CRT monitor with 640x480 screen resolution and a 60 Hz refresh rate.

Participants were instructed to focus on their own cardiac activity and silently count the number of heartbeats in three separate intervals of 25s, 35s and 45s. A start and stop signal corresponded with the beginning and end of an interval. The upcoming start signal of an interval was prompted by a question on the screen asking whether participants were ready. Almost immediately after the prompt, the start sound was presented together with a blank screen. After the stop signal, participants verbally reported the number of counted heartbeats during a resting period of 30 s, after which the prompt of the following interval was presented anew. The length of the intervals was not communicated to the participants, nor did they receive feedback on their performance. Importantly, during the heartbeat perception task, the use of physical manipulations (e.g. taking their pulse) to ease the counting was not allowed, and the experimenter monitored the participants through a camera.

A heartbeat perception score was derived in keeping with previous studies (Herbert et al., 2007; Pollatos, Kirsch, & Schandry, 2003; Pollatos, Matthias, & Schandry, 2007): per interval a difference score of the number of recorded and counted heartbeats was calculated. These difference scores were then divided by the number of recorded heartbeats, subtracted from 1, summed and averaged by the number of intervals. Due to this formula: $1/3\ \Sigma\ (1 - (|\text{recorded heartbeats} - \text{counted heartbeats}|) / \text{recorded heartbeats})$, the heartbeat perception score could vary between 0 and 1, with higher scores indicating higher IA and thus a small difference between counted and recorded heartbeats.

The heartbeat perception task was administered twice, at the beginning and end of the testing session. A mean heartbeat perception score was calculated by summing both

heartbeat perception scores (acquired at the beginning and end of the testing session), and dividing that sum by two.

The electrocardiogram was recorded via two external electrodes from the Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands), placed on the left lower and upper rib cage. R-waves were counted offline by means of a custom-made R-top algorithm in Brain Vision Analyzer 2 software.

Body Perception Questionnaire. Participants completed the Dutch translation of the Body Perception Questionnaire (Porges, 1993), a subjective self-report measure of IA. This questionnaire consists of four different subscales with a total of 96 items. The subscale of interest for our study was the awareness subscale, which consists of 45 items (Cronbach's α: .97 for both groups), questioning how aware participants are of their autonomic signals (e.g., swallowing frequently, how hard my heart is beating). Although this subscale was of main interest for our study, the other subscales (stress response; reactivity of the autonomic nervous system; stress style) of the BPQ were included to check for specificity. Items are rated on a five-point Likert scale, ranging from 1 (*never*) to 5 (*always*). The mean score of each subscale was obtained by summing all responses and dividing the sum by the number of items in the subscale.

Procedure

Participants were seated in a sound-attenuated and dimly lit room, sitting approximately 60 cm in front of the computer screen. Each participant signed an informed consent prior to participation in the experiment and received monetary compensation for their participation. This study was part of a larger experimental set-up. Two other behavioral tasks with a total duration of 50 min were administered in between both administrations of the heartbeat perception task; the results of these tasks will be reported elsewhere. Verbal as well as written instructions were given prior to the start of each task. This study was approved by the local ethics committee.

Data analysis

ANOVAs with group (ADHD vs. control) as between-subjects factor were performed to compare performance between groups on the heartbeat perception task, and the subjective measure of IA as indexed by the mean score of the awareness subscale of the

BPQ. To check for specificity, we also performed ANOVAs on the mean scores of the other subscales of the BPQ. Finally, links between the IA indices and symptoms of anxiety, depression, and alexithymia were explored by additional correlational analyses.

RESULTS

Performance on the heartbeat perception task

For both groups, the heartbeat perception score obtained at the beginning of the session correlated significantly with the heartbeat perception score acquired at the end (ADHD: $r = .80$, $p < .001$; control: $r = .92$, $p < .001$), indicating that the estimate of IA was reliable. Moreover, mean heartbeat perception scores obtained were comparable to previous studies (e.g., Herbert et al., 2007; Pollatos et al., 2007). For the ADHD group, the mean heartbeat perception score was .81 (range: .45 - .97), while it was .83 (range: .45 - .97) in the control group. The between-group comparison in mean heartbeat perception score yielded no significant results ($F(1, 46) = 0.23$, $p = .634$). Data are reported in Table 1, separately for the two groups.

As previous research has indicated worse IA as indexed by the heartbeat perception task in females versus males (Ehlers & Breuer, 1992), an additional ANOVA was performed with group (ADHD vs. control) and gender as between-subjects factors. This did not change the findings, as neither the main group effect ($F(1, 46) = 0.22$, $p = .641$), nor the group by gender effect ($F(1, 46) = 0.02$, $p = .902$) was significant. The main effect of gender was also not significant ($F(1, 46) = 0.03$, $p = .859$).

No significant correlations between alexithymia, anxiety or depression scores and the mean heartbeat perception score were observed, neither in the ADHD group (alexithymia: $r = .05$, $p = .805$; depression: $r = -.04$, $p = .866$; anxiety: $r = -.09$, $p = .649$), nor in the control group (alexithymia: $r = -.18$, $p = .412$; depression: $r = .02$, $p = .922$; anxiety: $r = -.05$, $p = .815$).

Body Perception Questionnaire

The between-group comparison of the score obtained on the awareness subscale yielded no significant results ($F(1, 46) = 1.41$, $p = .24$). Although groups did not differ on

the subscale measuring awareness, adults with ADHD scored higher on the other three subscales of the BPQ, namely stress response ($F(1, 46) = 10.84$, $p = .002$), reactivity of the autonomic nervous system ($F(1, 46) = 6.81$, $p = .012$), and stress style ($F(1, 46) = 5.85$, $p = .020$, see Table 1).

No significant correlations between alexithymia, anxiety or depression scores and the score on the awareness subscale were found, neither in the ADHD group (alexithymia: $r = .14$, $p = .518$; depression: $r = .16$, $p = .467$; anxiety: $r = .19$, $p = .356$), nor in the control group (alexithymia: $r = -.13$, $p = .546$; depression: $r = .11$, $p = .604$; anxiety: $r = .27$, $p = .206$).

Table 1. Scores on the objective and subjective measure of interoceptive awareness, separated per group

	ADHD	Control
Objective measure		
Heartbeat perception score 1	.78 (.16)	.81 (.17)
Heartbeat perception score 2	.83 (.15)	.86 (.14)
Mean heartbeat perception score	.81 (.15)	.83 (.15)
Average heart rate (bpm)	68.39 (9.59)	68.61 (10.76)
Subjective measure		
Awareness	2.35 (0.80)	2.08 (0.73)
Stress Response	2.85 (0.79)	2.20 (0.55)
Reactivity of the ANS	1.68 (0.43)	1.40 (0.30)
Stress Style	2.62 (0.57)	2.29 (0.35)

Note. Values are shown as means (*SD*). bpm = beats per minute.

DISCUSSION

As information regarding the momentary bodily state is of crucial importance for effective state regulation, state regulation deficits observed in ADHD may be associated with an inability to become aware of the bodily signals that provide information on the current energetic state. Surprisingly, this hypothesis has not yet been tested. The aim of the present study was thus to investigate IA in (adult) ADHD by means of an objective and subjective measure. The heartbeat perception task was administered to gain an objective measure of IA, while a questionnaire was used (the awareness subscale of the BPQ) to assess a self-report measure of IA. Performance on the heartbeat perception task was strikingly similar in adults with ADHD compared to healthy controls. Adults with ADHD and typically developed adults also did not differ on the self-report measure of IA. Findings therefore suggest a preserved monitoring of bodily state in adult ADHD, which tentatively suggests that the state regulation deficit and related self-regulatory difficulties in ADHD may not be due to an inability to monitor the current state.

Several possible reasons for this null-result can be formulated. For instance, it could be related to the paradigm used in the current study. However, this suggestion is doubtful since the heartbeat perception task which we applied is a well-validated and widely used paradigm to assess IA in different domains (e.g., Garfinkel et al., 2015; Herbert et al., 2007; Pollatos et al., 2007; Werner et al., 2013) and has previously been shown to be sensitive enough to uncover differences in IA in other clinical groups (e.g., anxiety and depression: Paulus & Stein, 2010). Moreover, it has been validated in neuroimaging research showing enhanced activity of the anterior insula during this task (Critchley et al., 2004). Also, the scores are comparable to scores from previous studies using the same paradigm (e.g., Herbert et al., 2007; Pollatos et al., 2007) and these scores furthermore indicate that both groups were able to perform well above chance level. Furthermore corroborating our finding is the striking similarity in variance of the mean heartbeat perception scores between both groups. In addition, comparing only the heartbeat perception score acquired at the beginning of the session between groups, gave the same null result, excluding the possibility that learning effects across both sessions of the task explain the findings. Moreover, preserved IA in ADHD was

confirmed by the self-report measure of IA, the awareness scale of the BPQ (Porges, 1993).

Other factors previously shown to be related to IA could have potentially obscured our findings. Alexithymia, anxiety and depression have been (differently) related to IA (Herbert et al., 2011; Paulus & Stein, 2010; Pollatos, Traut-Mattausch, et al., 2007). In the current study, groups did not differ for symptoms of anxiety, but adults with ADHD reported more symptoms of depression and alexithymia. However, correlations between indices of these factors and scores on both measures of IA were negligible in both groups, suggesting no association between IA and those constructs in our sample. Moreover, as alexithymia has previously been shown to be negatively associated with IA (Herbert et al., 2011), higher alexithymia symptoms in ADHD would result in lower IA in adults with ADHD and cannot explain the absence of a difference in IA between groups. The same reasoning holds for the elevated depression symptoms in ADHD. For mild to moderate levels of symptoms of depression, a negative relation has been reported between IA and symptoms of depression (Harshaw, 2015). Most participants in the ADHD group had non-clinical scores for depression on the ASR (Achenbach & Rescorla, 2003). Hence, more symptoms of depression could contribute to lower IA in ADHD, but cannot explain similar IA ability. Anxiety on the other hand has been positively correlated with IA (Paulus & Stein, 2010; Pollatos, Traut-Mattausch, et al., 2007). Thus, elevated levels of anxiety could have resulted in elevated IA in the ADHD group. This factor is however highly unlikely to explain the findings, because the groups did not differ on anxiety symptoms and anxiety was not found to be correlated with IA. To further exclude this possibility, we repeated the analyses without ADHD participants with elevated anxiety symptoms (one participant with a clinical score and two participants with a subclinical score), which did not alter the findings.

ADHD is a heterogeneous neurodevelopmental disorder and we are aware that the findings may not generalize to all individuals with ADHD. Both adults with ADHD predominantly inattentive and combined subtype were included in the study. It would be of interest to test for differences in IA between subgroups or subtypes of ADHD, however, in our study, this was not possible as separate groups were not large enough. Also both men and women with ADHD were included. Groups were however carefully matched on gender and additional analyses showed no influence of gender. With regard

to severity of ADHD symptoms, we feel confident that we tested a representative sample of adults with ADHD. All participants had a formal clinical diagnosis provided by a multidisciplinary team including a psychiatrist and this diagnosis was confirmed by a clinical interview (DIVA; Diagnostisch Interview Voor ADHD bij Volwassenen 2.0, Kooij & Francken, 2010). Also, although adults with ADHD did not differ on the awareness subscale of the BPQ, they were found to have more difficulties in autonomic reactivity, stress response and stress style (the other subscales of the BPQ), which is in line with previous research in adults with ADHD, in which elevated physiological stress responses and higher self-reported stress were observed (Combs, Canu, Broman-Fulks, Rocheleau, & Nieman, 2012; Hirvikoski, Lindholm, Nordenström, Nordström, & Lajic, 2009; Lackschewitz, Hüther, & Kröner-Herwig, 2008). Nonetheless, as to our knowledge this is the first study on IA in ADHD, further research is warranted to replicate our findings in other samples as well as in children with ADHD before final conclusions on IA in ADHD can be formulated.

The findings suggest that the basic skill of IA is intact in ADHD during a simple heartbeat perception task, but this does not rule out the possibility that becoming aware of bodily signals might be disrupted during other tasks or in daily life, perhaps as a result of reduced attention or distraction. From another perspective, it could be that IA in ADHD is preserved also in other situations, but that interoceptive information is wrongly applied or interpreted by this patient group. In other words, they might be able to monitor the momentary body state but are not able (or willing) to use the available information sufficiently. This can be further explored in future studies. The finding of preserved IA in ADHD instigates the debate on whether the self-regulatory difficulties in ADHD reflect a difficulty in allocating the required effort or are related to a general altered motivational style (Luman et al., 2010; Sonuga-Barke et al., 2010). Further research is needed to examine these hypotheses.

Some limitations have to be mentioned. First, as this is the first study investigating IA in ADHD and ADHD is known to be a heterogeneous disorder, generalization to other samples with ADHD is difficult. Replication of these findings is thus warranted. Second, although the heartbeat perception task we used is a well-validated task that has been extensively applied in previous research, it would be informative if results hold for other heartbeat perception paradigms, such as a heartbeat discrimination task (e.g.,

Whitehead, Drescher, Heiman, & Blackwell, 1977). Third, individuals with ADHD with and without use of medication (methylphenidate) were included in the study. Although we asked participants to interrupt their medication 48 hr prior to participation, in line with a lot of existing studies, it cannot be fully excluded that medication use may have influenced our findings. An exploratory data check did however not indicate a difference in IA scores between individuals with ADHD who were or not were taking methylphenidate in daily life.

In summary, following previous research inspired by the SRD model that unequivocally provided support for deficient regulation of energetic state in ADHD (Börger & van der Meere, 2000; Metin et al., 2012; Wiersema, van der Meere, Antrop et al., 2006; Wiersema, van der Meere, Van Coster et al., 2006), the hypothesis was put forward that the ability to monitor the momentary bodily state may be impaired in ADHD, a hypothesis that had been overlooked in previous research. However, no support was rendered for altered IA in adults with ADHD. The finding of preserved monitoring of bodily state tentatively suggests that self-regulatory difficulties in ADHD may not be related to a lack of information on the current state.

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CHAPTER 4

EVENT-RELATED BRAIN POTENTIALS REVEAL THE LOCUS OF ABNORMAL ERROR AWARENESS IN ADHD[1]

ABSTRACT

The current study investigated error awareness in adult ADHD. Adults with and without ADHD performed a speeded Go/No-Go task in which they were instructed to signal error commission by pressing an extra response button, while high-density EEG was recorded. Error awareness modulated the ERN and subsequent early and late Pe. The amplitude of the early Pe for aware errors was attenuated in adults with ADHD. Source localization analyses revealed this to be accompanied by decreased activation of the left superior/middle frontal gyrus and increased activation of the right inferior frontal gyrus. This latter activation was negatively correlated with the percentage of aware errors in the ADHD group. These findings suggest that ADHD influences error awareness via modulation of a specific neural network, where the right inferior frontal gyrus appears to be overactive. More generally, the results shed light on the neurophysiological time-course and brain basis of error awareness.

[1] Based on Godefroid, E., Pourtois, G., & Wiersema, J. R. (submitted). Event related brain potentials reveal the locus of abnormal error awareness in Attention Deficit Hyperactivity Disorder.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (*ADHD*) is an impairing neurodevelopmental disorder characterized by behavioral symptoms of inattention and/or hyperactivity/impulsivity that interfere with everyday life functioning in different settings (*DSM-5*; American Psychiatric Association, [APA] 2013). ADHD has a childhood onset but often persists into adulthood, with an estimated prevalence rate in adults of approximately 2.5% (Moffitt et al., 2015; Simon, Czobor, Bálint, Mészáros, & Bitter, 2009). Explanatory models of ADHD have moved beyond trying to find a fixed core deficit and define ADHD as a disorder of self-regulation, thereby putting emphasis on its dynamic, rather than fixed, nature (Nigg, 2005; Sergeant, 2005; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010; van der Meere, Börger, & Wiersema, 2010). Self-monitoring and adaptive control are prerequisites of effective self-regulation and ADHD has been associated with impairments in both components. Post-error slowing is seen as an index of behavioral adaptive control and a failure to slow down after error commission in ADHD has been interpreted as indicating deficient adaptive control (Balogh & Czobor, 2014). Event-related potential (ERP) studies on neurophysiological correlates of error processing in children and adults with ADHD have shown abnormalities in both the *error-related negativity* (*ERN*) and *error-positivity* (*Pe*), suggestive of impairments in both early and later stages of error monitoring and action control (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Shiels & Hawk, 2010).

The ERN is evoked rapidly after or during error commission (Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993) and is argued to reflect a mismatch between the actual and intended or desired action (Coles, Scheffers, & Holroyd, 2001; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000), post-response conflict (Carter et al., 1998), or reward prediction error (Holroyd & Coles, 2002). A similar negative deflection is observed after correct responses (albeit with a much smaller amplitude than the ERN), especially when speeded responses are executed or speed is emphasized (correct-related negativity: CRN; Ford, 1999; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000). The main neural generator of both potentials has been source-localized to posterior medial frontal cortex (pMFC; Debener et al., 2005; Dehaene, Posner, & Tucker, 1994). The ERN is thought to reflect automatic error

detection as it is elicited even when the participant remains unaware of making an error (Dhar, Wiersema, & Pourtois, 2011; Endrass, Reuter, & Kathmann, 2007; Nieuwenhuis, Ridderinkhof, Blow, Band, & Kok, 2001; Shalgi, Barkan, & Deouell, 2009; for review see Wessel, 2012). Initially, studies that manipulated error awareness mostly found that the ERN was insensitive to this factor (Endrass et al., 2007; Nieuwenhuis et al., 2001; O'Connell et al., 2007). However, later studies did find larger ERN amplitudes for aware compared to unaware errors (Godefroid, Pourtois, & Wiersema, 2016; Shani Shalgi & Deouell, 2012; Wessel, Danielmeier, & Ullsperger, 2011; see for review Wessel, 2012), suggesting that the ERN can be sensitive to error awareness, under certain circumstances.

The ERN is followed by the Pe, a large positive deflection occurring between 300 and 500 ms after the onset of the erroneous response with a more posterior parietal scalp distribution. Although the exact functional meaning of this component is still debated (Ridderinkhof, Ramautar, & Wijnen, 2009), it is often argued to reflect the conscious detection of an error, and is related in turn to specific cognitive or affective-motivational processes (Falkenstein, Willemssen, Hohnsbein, & Hielscher, 2005). In contrast to the ERN, the Pe is only elicited for errors that are consciously detected and is absent (i.e., amplitude close to zero baseline) when errors are made but go unnoticed (Dhar, Wiersema, & Pourtois, 2011; Endrass, Klawohn, Preuss, & Kathmann, 2012; O'Connell et al., 2007; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010). This mid-latency response-locked ERP component is therefore linked to error awareness, although it is not clear whether the Pe reflects the result (or accumulation of evidence process) of becoming aware of an error, or alternatively, it corresponds to the activation of processes that follow it (Ullsperger et al., 2010). Regarding the underlying brain generators of the Pe, sources in the pMFC and more posterior parietal regions, as well as in the insula have often been reported (Dhar, Wiersema, & Pourtois, 2011; Herrmann, Römmler, Ehlis, Heidrich, & Fallgatter, 2004; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007; O'Connell et al., 2007). It is important to note that the ERN is often followed by two distinct positive components and that the above findings relate to the so-called late Pe characterized by a centro-parietal scalp distribution and a peak latency ranging between 300 and 500 ms after error commission. Immediately after the ERN, another positive component usually occurs (that can be dissociated in

space and time from the late Pe), referred to as the early error positivity (O'Connell, Bellgrove, et al., 2009) or early Pe (Arbel & Donchin, 2009; Endrass, Klawohn, Preuss, & Kathmann, 2012; O'Connell, Dockree, et al., 2009), which has a more fronto-central distribution and hence precedes the late Pe. The early Pe is believed to be functionally (more) similar to the ERN (Debener et al., 2005; Luu, Tucker, & Makeig, 2004; Van Veen & Carter, 2002), although it has been shown to have a different topography than the ERN (Arbel & Donchin, 2009; Endrass et al., 2012).

With regard to ADHD and ERP correlates of error processing, only two studies previously made a distinction between the early and late Pe (O'Connell, Bellgrove, et al., 2009; Van De Voorde, Roeyers, & Wiersema, 2010), while all other studies focused on the ERN and did not distinguish between an early and late Pe, but mostly evaluated the Pe at central-parietal scalp locations. However, across these studies, discrepant results have been reported. In children with ADHD, the ERN has often but not always been found to be smaller, but the results seem to be most consistent for the Pe, with systematic smaller amplitudes in ADHD (for reviews see Johnstone, Barry, & Clarke, 2013; Shiels & Hawk, 2010), while in adults, the findings with regard to the Pe seem to be less consistent across studies (for a meta-analysis, see Geburek et al., 2013). There are many factors that may potentially account for this discrepancy (e.g., heterogeneity of ADHD, comorbidity, sample size, task difficulty, task duration). A striking finding in the meta-analysis recently performed by Geburek et al. (2013) was the differential effect of the type of task (flanker or Go/No-Go) applied on the reduction of the Pe in juveniles and adults with ADHD, with smaller Pe amplitudes apparent for Go/No-Go tasks, but not for flanker tasks. Interestingly, according to these authors, false alarms (i.e., an incorrect button press to a No-Go stimulus when no response was required) are more salient and more easily detected than flanker errors (i.e., a response was always required but a wrong response was given) as in the case of false alarms but not in the case of flanker errors, individuals can rely on their own covert reactions to become aware of their error. This observation suggests that the Go/No-Go task is a more ideal paradigm to investigate the emergence of error awareness than the flanker task. Alternatively, flanker errors likely reflect transient attentional lapses and/or reduced cognitive control, as opposed to a genuine break down in impulse control or inhibition in the case of false

alarms. It could therefore well be that ADHD is related to problems with motor response inhibition that leads to poorer conscious detection of errors.

A smaller Pe during error processing in ADHD has been argued to reflect reduced error awareness, however in order to relate this neurophysiological change in ADHD to (impaired) error awareness, a direct contrast between aware and unaware errors is absolutely needed. However, only one study so far has explored error awareness in (adults with) ADHD by using error verification during an error awareness task (O'Connell, Bellgrove, et al., 2009). In this earlier study, adults with ADHD generally made more errors than controls, but were less likely to report these errors, which suggests an error awareness deficit. The ERN amplitude was not modulated by error awareness, nor by ADHD. Crucially, the amplitude of the late Pe to aware errors was selectively reduced in ADHD adults compared to typically developed adults. Complementary source localization results indicated the contribution of both rostral ACC and posterior cingulate/precuneus regions for the late Pe in the control group, while activation in the former region was not observed in the ADHD group, eventually explaining the attenuated late Pe amplitude to aware errors in this group. Moreover, a smaller early Pe was found in ADHD, however, irrespective of error awareness.

The main aim of this study was to examine error awareness in adult ADHD by means of a standard paradigm including an (extra) error verification task embedded in a speeded Go/No-Go task. This enabled us to explicitly contrast aware and unaware errors. Based on findings of O'Connell, Bellgrove, et al. (2009), we hypothesized fewer aware errors and a smaller late Pe to aware errors in ADHD adults compared to a gender- and age-matched group of typically developed adults. In addition, we expected to observe an unchanged ERN but smaller early Pe, regardless of error awareness, in ADHD adults when compared to controls.

METHOD

Participants

Twenty-five adults with ADHD participated in this study (age: *M*(*SD*) = 24.04 years (*5.26*); 12 females, one left-handed). The initial control group consisted of 32 typically

developed participants (age: *M*(*SD*) = 23.00 years (*2.97*), 17 females, five left-handed). In the control group, 10 participants were excluded due to an insufficient number of error trials for ERP analyses (Olvet & Hajcak, 2009). Results are reported for the remaining 22 control participants (age: *M*(*SD*) = 22.50 years (*2.33*), 11 females, five left-handed), matched on age ($F(1, 46) = 1.60$, $p = .212$), sex ($\chi^2(1) = 0.20$, $p = .654$) and IQ ($F(1, 46) = 3.24$, $p = .079$) with the ADHD participants.

Individuals with ADHD were recruited through staff members, advertisements, self-support groups for ADHD and selected from a local database (adults with ADHD who participated in previous research). All adults with ADHD had a formal (clinical) diagnosis established by a certified psychiatrist and completed a semi-structured clinical interview to confirm diagnosis (DIVA; Diagnostisch Interview voor ADHD bij Volwassenen 2.0, Kooij & Francken, 2010). For diagnosis confirmation in childhood and adulthood, respectively six or four, out of nine DSM-criteria of inattention and/or hyperactivity and impulsivity had to be met. Adults with ADHD using stimulants were asked to interrupt their medication 48 hr prior to participation in the experiment. Eight adults with ADHD were currently taking medication, while four participants had never taken medication. Thirteen participants occasionally took medication during exam periods or important work-related projects. Control participants were recruited through an online database and advertisements. Exclusion criteria for all participants were an estimated IQ below 75, history of brain-related illness or neurological disorder and a clinical diagnosis of depression or autism spectrum disorder. Control participants were excluded if they met more than six criteria in the attentive or hyperactive/impulsive domain, both in childhood and adulthood, as evaluated by the Zelfrapportage Vragenlijst voor Aandachtsproblemen en Hyperactiviteit (ZVAH; Kooij et al., 2010). Comorbidity in the adult ADHD group was low and variable, and included anxiety disorder (n = 1), dyslexia (n = 4), dysgraphia (n = 1), and dyscalculia (n = 4).

Both groups completed an abbreviated version (Meyers, Zellinger, Kockler, Wagner, & Miller, 2013) of the WAIS-IV (Wechsler Adult Intelligence Scale-IV; Wechsler, 2008), except for the individuals with ADHD who were recruited through the local database since they had already completed the same abbreviated version (Ryan & Ward, 1999) of the WAIS-III (Wechsler, 1997) in a previous study. Not unexpectedly, the adult ADHD group actually scored significantly higher on the WURS (Wender Utah Rating Scale;

Wender, Ward, & Reimherr, 1993), a measure of presence of childhood ADHD, than the control group ($F(1, 46) = 66.33$, $p < .001$). In addition, the adult ADHD group scored significantly higher on the DSM oriented ADHD scale of the ASR (Adult Self-Report; Achenbach & Rescorla, 2003) than the control group ($F(1, 46) = 28.07$, $p < .001$). Adults with ADHD did not report higher substance abuse ($F(1, 46) = 3.39$, $p = .072$) or anxiety ($F(1, 46) = 0.20$, $p = .657$), as measured with the DSM oriented scales of the ASR. They scored marginally significantly higher on the DSM oriented depression scale of the ASR ($F(1, 46) = 3.97$, $p = .052$). Sample characteristics are reported in Table 1.

Table 1. Sample characteristics

	ADHD	Control
IQ	103.72 (12.86)	111.09 (15.23)
DIVA: ADHD C/I	16/9	-
ZVAH: adulthood		
Inattention	6.52 (2.12)	1.86 (1.94)
Hyperactivity/Impulsivity	4.52 (2.73)	1.27 (1.35)
WURS	51.36 (14.04)	22.36 (11.14)
ASR		
ADHD	74.64 (11.90)	58.27 (8.81)
Substance abuse	57.60 (6.51)	54.36 (5.40)
Anxiety	56.24 (6.23)	55.36 (7.20)
Depression	60.40 (9.22)	55.45 (7.52)

Note. Values are shown as means (*SD*). IQ = measured with *Wechsler Preschool and Primary Scale of Intelligence – Fourth edition*, DIVA = *Diagnostisch Interview voor ADHD bij Volwassenen* 2.0, C = combined subtype, I = inattentive subtype, ZVAH: *Zelfrapportage Vragenlijst voor Aandachtsproblemen en Hyperactiviteit,* WURS = *Wender Utah Rating Scale,* ASR = *Adult Self-Report*.

Speeded Go/No-Go task

Stimuli were colored squares, presented on a black background and subtending 4.7 degrees of visual angle. All stimuli were presented foveally. According to the hue-saturation-value color system, color is classically defined by three concurrent parameters: hue (0-360), saturation (0-100) and value (0-100). To create different color tints, saturation and value were kept constant (both at 100), while hue was varied systematically. Two different spectra of tints were created: (a) the orange spectrum (0 to

60), with red (0) and yellow (60) as extreme colors, and (b) the purple spectrum (240 to 300) with blue (240) and pink (300) as extreme colors. A pilot study revealed that 6 participants were able to distinguish the tints of these spectra. Participants performed a Go/No-Go task, in which a cue always preceded a target. On 60% of the trials (Go trials), cue and target (Go stimulus) had the same tint, requiring a speeded button press. Possible cue-target pairs in the Go trials were red-red (0), yellow-yellow (60), blue-blue (240) or pink-pink (300). On the remaining 40% of trials (No-Go trials), cue and target (No-Go stimulus) differed in tint, requiring active inhibition of the prepotent response tendency.

For the No-Go stimulus, two difficulty levels (easy and difficult) were created. Easy and difficult No-Go trials were randomly intermixed. In the easy condition, cue and (No-Go) target stimuli were relatively easy to distinguish from each other. The difference in tints of cue and No-Go stimulus covered 25 points along the spectrum. Possible cue-target pairs were orange (25) – orange (50), orange (35) – orange (10), purple (265) – purple (290) and purple (275) – purple (250). In the difficult condition, the tints of the cue and (No-Go) target stimuli were harder to discriminate from one another, because the difference in tints covered only 10 points along the same axis. Possible cue-target pairs were red (0) – orange (10), yellow (60) – orange (50), blue (240) - purple (250) and pink (300) – purple (290). Note that No-Go (target) stimuli were matched across conditions such that all elicited response-locked ERP (cf. contrast between correct and incorrect responses) could not be imputed simply to uncontrolled changes in the physical appearance of these stimuli across conditions.

Participants were instructed to respond as accurately and rapidly as possible when the target (Go) stimulus was physically identical to the cue (i.e., having the same perceived color) by pressing the response button on a response box with the index finger of their dominant hand, but to withhold responding when they did not match in color (No-Go). Participants were also asked to report explicitly their errors whenever they felt they had violated this simple rule (i.e., push the go button while the stimulus was actually a No-Go). Error commission had to be indicated by pressing a second verification button as soon as possible following its detection (using a separate key of the response box located to the left of the main response button to which participants had to make a lateral movement with the response finger). Task instructions emphasized

accuracy and speed. An individually calibrated response limit was set for Go stimuli to induce time pressure and in turn increase error commission, hence taking the actual and subject-specific RT speed into account. At the start of every block, the initial response limit was set at 350 ms. For every participant individually, the limit was adjusted by means of an algorithm and updated online for every (subsequent) trial. This algorithm has already been used previously extensively (Aarts & Pourtois, 2010; Dhar et al., 2011; Koban, Pourtois, Vocat, & Vuilleumier, 2010; Pourtois et al., 2010). In short, the current RT is compared against the updated RT limit, which corresponds to the average of this RT and the preceding RT. If the participant happens to respond above this limit (slow hit), a negative feedback is presented, while if he happens to respond below this limit (fast hit), no feedback is presented.

Due to the manipulated difficulty of the No-Go trials and the induced time pressure, the task resulted in a sufficient number of aware errors and unaware errors, in addition to hits. Aware errors were defined as responses to No-Go stimuli that were followed by overt verification. Unaware errors were defined as responses to No-Go stimuli that were not followed by overt detection. Hits were defined as correct responses to Go stimuli, regardless of their actual speed (fast and slow hits were collapsed; see Aarts, De Houwer, & Pourtois, 2013 for a similar approach).

A trial started with a white fixation cross (visual angle of 0.5 degrees) presented for 1500 ms, after which the cue appeared for 500 ms. Prior to target presentation, a variable delay (randomly varying between 500 and 1000 ms) was introduced, precluding target anticipation. The target remained visible until a response was given, with a maximum duration of 1000 ms. After target presentation, the course of the trial depended on the target's identity (Go or No-Go). When the participant made a fast hit or omitted a response to a Go stimulus, a black screen was shown for 1500 ms. In case of a slow hit, after a delay of 500 ms, a feedback screen indicating that participants were too slow was presented for 500 ms. When participants withheld responding to a No-Go stimulus, the black screen was presented again. In case of an error, they had 1500 ms to press the verification button during which a black screen was presented (see Figure 1).

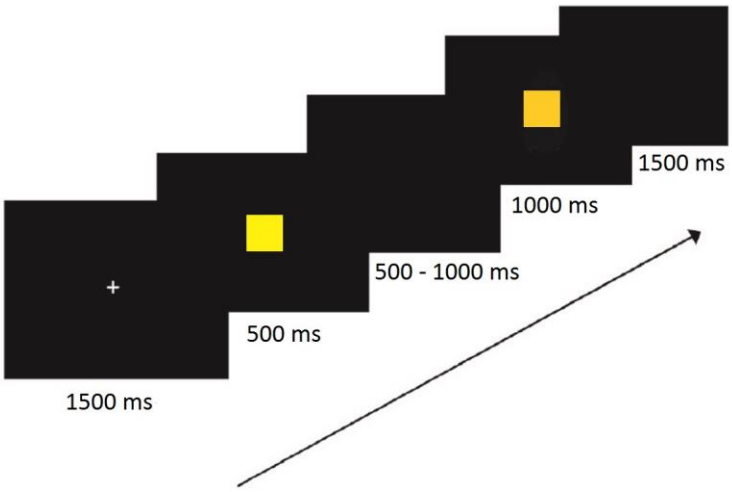

Figure 1. Example of a No-Go trial. After error commission, participants had 1500 ms to indicate (by means of an additional key press) error awareness.

Twelve practice trials were administered at the beginning of the experiment to familiarize the participants with the manipulation of tints and to ensure they understood the instructions properly. The task consisted of 6 blocks, each block containing 36 Go trials and 24 No-Go trials, with a total of 360 trials (216 Go trials, 72 No-Go trials in the easy condition, 72 No-Go trials in the difficult condition). A short break was introduced between two consecutive blocks. The total duration of the task was about 35 minutes.

Procedure

The task was programmed using E-Prime 2.0 software (http://www.pstnet.com/products/e-prime/) and presented on a 19-inch CRT monitor with 640x480 screen resolution and a 60Hz refresh rate. Participants were seated in a sound-attenuated, dimly lit and electrically shielded room, sitting approximately 60 cm in front of the computer screen. Each participant signed an informed consent prior to participation in the experiment and were compensated 32.5 Euro for it. The study was approved by the local ethics committee of the Faculty of Psychological and Educational Sciences, Ghent University.

This study was part of a larger experimental set-up. The Go/No-Go task was administered together with other behavioral tasks, but the results of these tasks will be reported elsewhere. The order of the tasks was counterbalanced.

EEG acquisition and data reduction

The electroencephalogram (EEG) was continuously recorded at a 1024 Hz sampling rate with a 128-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands). The signal was referenced online to a CMS-DRL ground. Vertical EEG was recorded from infraorbital and supraorbital electrodes placed in line with the pupil of the right eye, while horizontal EEG was acquired through electrodes positioned on the outer cantus of each eye. Data was referenced offline against the average reference and down-sampled to 512 Hz sampling rate. A low pass filter of 80 Hz, a high pass filter of 0.25 Hz and 50 Hz Notch filter were applied. By means of the method of Gratton and colleagues (Gratton, Coles, & Donchin, 1983) the signal was corrected for blinks. ERPs of interest were computed offline with Brain Vision Analyzer 2.0 (Brain Products, GmbH, Munich, Germany). Segmentation was performed relative to response onset with an interval ranging from 200 ms before to 1000 ms after response onset. Each segment was baseline corrected to the entire pre-response onset interval. Artifacts were semi-automatically detected and rejected with a fixed ± 100 µV criterion relative to baseline. Noisy electrodes were interpolated using a spherical spline procedure (order of spline = 4). We computed individual averaged data for correct (hits) and incorrect responses, separately for aware and unaware errors. Finally, a 30 Hz low-pass filter was applied on the individual averaged data for smoothing purposes. Grand average waveforms were computed separately for the three main conditions (hits, aware errors, unaware errors).

Data analysis

Performance. Two-tailed independent samples *t*-tests were performed to compare groups on performance data. Omissions were defined as omitted responses to Go stimuli. Hit RT was defined as the average reaction time of correct responses to Go stimuli. Hit SD-RT was calculated as the average standard deviation of the hit RT per participant. Percentage of aware errors is the ratio of the number of aware errors to the total number of commission errors (multiplied by 100).

Electrophysiological measures. In line with previous ERP studies investigating error processing and awareness (Dhar et al., 2011; O'Connell, Bellgrove, et al., 2009), an early negative deflection (CRN to correct responses and ERN to errors) was elicited at fronto-

central sites. An early Pe and late Pe were evoked for aware errors exclusively, at central sites and at centro-parietal sites, respectively. Based on the obvious topographical properties of the present data set, the mean amplitudes of the ERN and the early Pe were defined, respectively, between 0 and 80 ms at FCz and between 100 and 300 ms at Cz. As the distribution of the late Pe was spread across centro-parietal and more parietal sites, the mean amplitude of the late Pe was calculated at CPz and Pz between 300 and 500 ms following error commission, in line with the time window used in the study of O'Connell, Bellgrove, et al. (2009).

Amplitude values of the ERN and the early Pe were entered into mixed ANOVAs with the within-subjects factor outcome (3 levels: hits, aware errors and unaware errors) and the between-subjects factor group (2 levels: ADHD vs. control). Mixed ANOVAs with the within-subjects factors outcome (3 levels: hits, aware errors and unaware errors) and electrode (2 levels: CPz and Pz) and the between-subjects factor group (2 levels: ADHD vs. control) were performed on the amplitude values of the late Pe. When sphericity assumptions were violated as indicated by a Mauchly test, Greenhouse-Geisser corrections were used. Amplitude values of the ERN, early Pe and late Pe for aware errors vs. unaware errors, aware errors vs. hits, and unaware errors vs. hits were submitted to a priori planned and orthogonal contrasts, with stringent Bonferroni corrections used wherever appropriate. If a group by outcome interaction was revealed, it was followed up by independent samples *t*-tests on the difference scores between outcomes (aware errors minus unaware errors, aware errors minus hits, unaware errors minus hits). Figure 2 shows the grand average waveforms at FCz, Cz and CPz, for hits, aware errors, and unaware errors, separately for the ADHD and control group.

Source localization. When significant outcome by group interactions were identified at the scalp level by the previous ERP analyses, the underlying configuration of neural/cortical generators giving rise to these effects were estimated by means of a specific distributed linear inverse solution, namely standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002). sLORETA computes the smoothest of all possible activity distributions (i.e. no a priori assumption is made on the number and locations of the sources), based on the neurophysiological assumption of coherent coactivation of neighbouring cortical areas (Silva, Amitai, & Connors, 1991). sLORETA solutions are computed within a three-shell spherical head model co-registered

to the MNI152 template (Mazziotta et al., 2001). The source locations were therefore given as (x, y, z) coordinates (x from left to right; y from posterior to anterior; z from inferior to superior). sLORETA estimates the 3-dimensional intracerebral current density distribution in 6239 voxels (5 mm resolution). Source localization analyses were performed on a slightly smaller sample, because the data of three participants were found to be too noisy and they led to aberrant solutions (ADHD: n = 23, control: n = 21).

RESULTS

Behavioral results

The (descriptive) behavioral data are reported in Table 2, separately for the two groups. The two groups differed regarding the number of omissions ($t(45) = 2.22$, $p = .032$, $d = 0.67$), hit RT ($t(45) = 2.02$, $p = .049$, $d = 0.59$), and hit SD-RT ($t(45) = 2.34$, $p = .024$, $d = 0.68$). They did not differ on the number of unaware errors ($t(45) = -0.80$, $p = .427$, $d = 0.24$), aware error RT ($t(45) = 1.56$, $p = .125$, $d = 0.46$), or unaware error RT ($t(45) = 1.67$, $p = .102$, $d = 0.49$).

Contrary to our predictions, no group difference was found for the number of aware errors ($t(45) = 0.41$, $p = .682$, $d = 0.12$), or the percentage of aware errors ($t(45) = 0.67$, $p = .507$, $d = 0.20$).

Table 2. Behavioral data of the error awareness task for the ADHD and control group

	ADHD	Control
Number of omissions	8.80 (13.09)	2.41 (3.51)
Hit RT (ms)	286.11 (27.72)	271.22 (22.03)
Hit SD-RT	63.54 (7.91)	57.40 (10.08)
Number of aware errors	14.80 (11.72)	13.50 (9.56)
Percentage of aware errors	21.32 (14.55)	18.65 (12.50)
Number of unaware errors	56.84 (16.49)	60.41 (13.65)
Aware error RT (ms)	294.33 (54.36)	272.58 (38.53)
Unaware error RT (ms)	306.24 (50.78)	284.81 (34.52)

Note. Values are shown as means (*SD*).

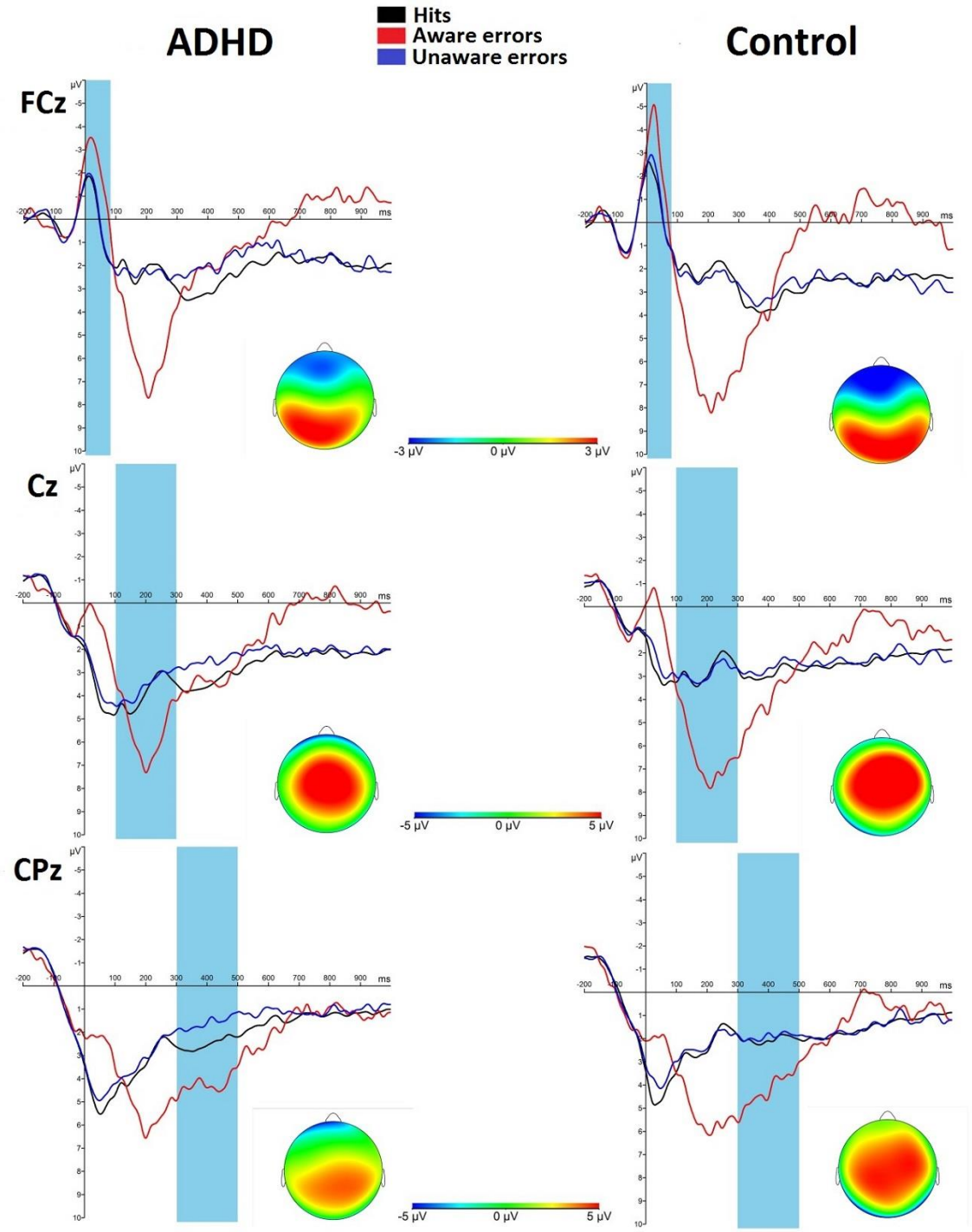

Figure 2. Grand average response-locked ERP waveforms at FCz, Cz and CPz for hits, aware errors and unaware errors, separately for the ADHD and control group. The topographical maps (horizontal view) correspond to the time windows of the ERN for aware errors (0-80 ms), the early Pe for aware errors (100-300 ms) and the Pe for aware errors (300-500 ms).

ERP results

For the ERN, the main effect of outcome ($F(2, 90) = 15.07$, $p < .001$, $\eta^2_p = .25$) was highly significant. The amplitude of the ERN was significantly larger for aware errors than hits ($p < .001$) or unaware errors ($p = .001$), while no difference was observed between hits and unaware errors ($p = .999$). The main effect of group ($F(1, 45) = 0.62$, $p = .437$, $\eta^2_p = .01$), and the interaction between outcome and group did not reach significance ($F(2, 90) = 0.10$, $p = .905$, $\eta^2_p < .01$).

For the early Pe, a significant main effect of outcome was revealed ($F(2, 90) = 34.68$, $p < .001$, $\eta^2_p = .44$). The amplitude of the early Pe was significantly larger for aware errors than for hits ($p < .001$) and unaware errors ($p < .001$), while no difference was evidenced between hits and unaware errors ($p > .999$). The main effect of group did not reach significance ($F(1, 45) = 0.20$, $p = .658$, $\eta^2_p < .01$). However, a significant interaction between outcome and group was revealed ($F(2, 90) = 4.34$, $p = .016$, $\eta^2_p = .09$). Independent samples *t*-tests performed on the difference scores between aware and unaware errors showed a marginally significant group difference ($t(45) = -1.93$, $p = .060$, $d = 0.55$) with a larger error awareness effect in the control group than in the ADHD group. In addition, the difference score between aware errors and hits was significantly larger in the control group compared to the ADHD group ($t(45) = -2.33$, $p = .025$, $d = 0.68$), while the unaware errors – hits difference was not ($t(45) = -1.09$, $p = .281$, $d = 0.33$).

With regard to the late Pe, the main effect of outcome reached significance ($F(2, 90) = 16.83$, $p < .001$, $\eta^2_p = .27$). The amplitude of the late Pe was significantly larger for aware errors than hits ($p = .001$) or unaware errors ($p < .001$), while no difference was evidenced between hits and unaware errors ($p = .257$). A significant main effect of electrode was revealed ($F(1, 45) = 16.83$, $p < .001$, $\eta^2_p = .32$). The main effect of group did not reach significance ($F(1, 45) = 0.11$, $p = .748$, $\eta^2_p < .01$), nor did the two-way interactions between outcome and group ($F(2, 90) = 0.38$, $p = .684$, $\eta^2_p = .01$), electrode and group ($F(1, 45) = 0.51$, $p = .478$, $\eta^2_p = .01$), outcome and electrode ($F(2, 90) = 2.21$, $p = .115$, $\eta^2_p = .05$), or the three-way interaction ($F(2, 90) = 0.67$, $p = .514$, $\eta^2_p = .02$).

Although no significant interaction with the factor electrode was revealed for the analysis of the amplitude of the late Pe, we performed additional mixed ANOVAs with the within-subjects factor outcome (3 levels: hits, aware errors and unaware errors) and

the between-subjects factor group (2 levels: ADHD vs. control) on the amplitude values of the late Pe, only at CPz, to enable a direct comparison with the study of O'Connell, Bellgrove, et al. (2009) in which the late Pe was analyzed at CPz only. A main effect of outcome was found ($F(2, 90) = 8.93$, $p = .003$, $\eta^2_p = .17$), however the main group ($F(1, 45) = 0.01$, $p = .919$, $\eta^2_p < .001$) and interaction with group effects ($F(2, 90) = 0.20$, $p = .822$, $\eta^2_p < .01$) were not significant.

Source localization results

Source reconstruction of the ERN, early Pe and late Pe to aware (as opposed to unaware) errors was performed, for the control group specifically, to establish partly non-overlapping networks giving rise to these three consecutive response-locked ERP components (see Figure 3A). For the ERN, a main dorsal ACC generator (BA 6, x = -6, y = 5, z = 70, *t*-value = 1.33) as well as activation in the occipital lobe (BA17/18, x = -20, y = -95, z = -20, *t*-value = 2.57) were found. For the early Pe, a dorsal ACC source similar to the source found for the ERN (BA 6, x = -5, y = 5, z = 60, *t*-value = 9.87) was observed together with posterior cingulate activation (BA23/30, x = -5, y = -29, z = 26, *t*-value = 1.6). For the late Pe, a generator in the inferior parietal lobule (BA 40, x = -49, y = -38, z = 56, *t*-value = 5.38) was evidenced.

As the ERP results indicated a group difference in error awareness for the early Pe, additional source localization analyses were performed for this component. In ADHD, for the early Pe, a dorsal ACC (BA 6) generator very similar to the source found in the control group was found in response to aware errors (x = -5, y = 0, z = 60, *t*-value = 7.76, see Figure 3B). Source reconstruction of the error awareness effect (i.e., the difference score between aware and unaware errors) showed significant group differences for two non-overlapping clusters, one located in the left superior/middle frontal gyrus (lS/MFG; BA 8; *t*-value = -2.35, x = -4, y = 35, z = 55), and the other one in the right inferior frontal gyrus (rIFG; BA 47; *t*-value = 2.52, x = 51, y = 21, z = -6, see Figure 3C). These seeds were selected and the raw peak amplitudes of these seeds were extracted separately for each individual. Independent samples *t*-tests on the amplitude of these seeds were performed to examine possible differences between groups for the error awareness effect. A smaller error awareness effect in the ADHD compared to the control group was evidenced in the lS/MFG ($t(42) = -2.35$, $p = .024$, $d = 0.70$), while conversely, a

significantly larger error awareness effect was observed in the rIFG ($t(42) = 2.37$, $p = .023$, $d = 0.73$).

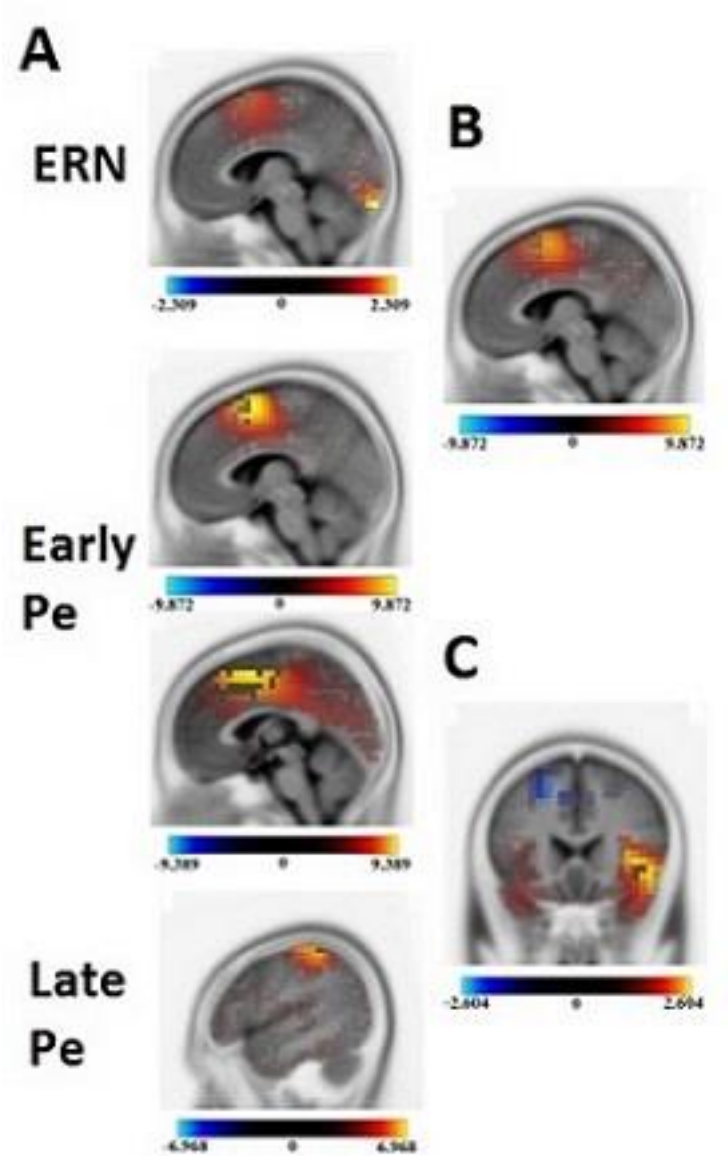

Figure 3. Source reconstruction. (A) Source reconstruction for the ERN, the early Pe and the late Pe to aware errors, for the control group. (B) Source reconstruction for the early Pe to aware errors showing a main dorsal ACC generator, for the ADHD group. (C) Source reconstruction revealing opposite effects in the lS/MFG and the rIFG. During the early Pe, a larger rIFG activation (blue/cold color) for error awareness was found for ADHD participants, while a larger lS/MFG activation (yellow/hot color) for error awareness was found for control subjects. lS/MFG = left superior/middle frontal gyrus, rIFG = right inferior frontal gyrus.

In addition, we found a significant negative (Pearson) correlation between the percentage of error awareness and the amplitude of the rIFG (r = -.45, p = .030) in the ADHD group (Figure 4), which was in the same direction but not significant in the control group (r = -.13, p = .586). No significant correlations were found between the lS/MFG's activity and the percentage of aware errors (ADHD: r = -.06, p = .784; control: r = -.19, p = .418). These analyses were repeated with Spearman correlations to exclude possible confounds from outliers and the results remained the same for the rIFG (ADHD: r_s = -.51, p = .013; control: r_s = -.07, p = .752) as well as the lS/MFG (ADHD: r_s = -.20, p = .359; control: r_s = -.12, p = .592).

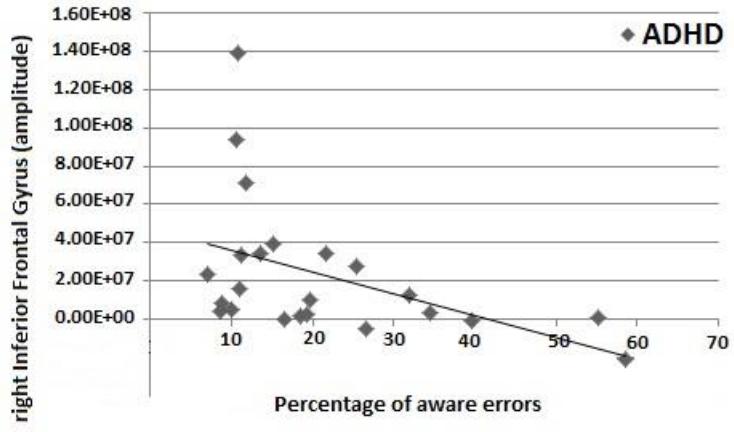

Figure 4. Scatter plot depicting the (Pearson) correlation between the percentage of aware errors and the amplitude values of the rIFG, for the ADHD group.

DISCUSSION

Earlier ERP studies showing a smaller Pe in ADHD already suggested diminished error awareness in this condition, even though only one of them actually contrasted aware to unaware errors and found direct evidence for this assumption (O'Connell, Bellgrove, et al., 2009). The aim of the current study was therefore to extend these earlier findings and examine error awareness in a large sample of carefully screened adult ADHD participants by means of high-density EEG recording, while they performed a speeded Go/No-Go task in which they were instructed to signal conscious error

detection using an extra button response. Our results show that in accord with ample previous evidence (Klein, Wendling, Huettner, Ruder, & Peper, 2006), individuals with ADHD were slower responders, made more errors of omission and were more variable in their responding than controls. However, contrary to one of our main predictions, there was no impaired error awareness at the behavioral level in adults with ADHD compared to controls. Notwithstanding this lack of group difference at the behavioral level in terms of error awareness, our ERP results suggested ADHD-related alteration in error awareness, as reflected primarily by a smaller error awareness effect (i.e., aware errors minus unaware errors) at the level of the early Pe, with corresponding changes in the underlying neural generators giving rise to this scalp effect.

Error awareness as accumulation of evidence

Irrespective of ADHD, error awareness reliably influenced the magnitude of the three ERP components of interest (ERN, early Pe and late Pe). Unlike O'Connell, Bellgrove, et al. (2009) who previously reported a larger ERN amplitude to errors, irrespective of their awareness, compared to correct responses, in the current study, at the same fronto-central sites, the ERN amplitude to aware errors was enhanced in comparison either to unaware errors or correct responses (i.e., the CRN component). The fact that the ERN to unaware errors and CRN to hits were equally large is in accord with ERP previous studies that used similar speeded paradigms (Aarts & Pourtois, 2010; Aarts, Vanderhasselt, Otte, Baeken, & Pourtois, 2013; Dhar et al., 2011) in which the use of the RT limit enhances uncertainty and impulsive responding (Pailing & Segalowitz, 2004). The finding of a larger ERN to aware errors implies that this early error-related activity is sensitive to error awareness, under specific conditions (Endrass et al., 2007; Godefroid et al., 2016; Nieuwenhuis et al., 2001; O'Connell et al., 2007; Shalgi & Deouell, 2012; Wessel et al., 2011; Wessel, 2012). Systematic changes of the ERN component as a function of error awareness appear to be dependent on the paradigm (and hence task demands) used, as well as the method that is devised to assess (subjective) error awareness (Shalgi & Deouell, 2012). For example, recently, we found evidence for modulation of the ERN by error awareness, but only when visual sensory feedback from the response hand was available (Godefroid et al., 2016).

Following the ERN, as expected, two conspicuous positive components related to errors (and their conscious detection) were recorded in our study, an early Pe at central sites, followed by a more centro-parietally distributed late Pe, in line with many previous ERP studies (Arbel & Donchin, 2009; Endrass et al., 2012; O'Connell et al., 2007; O'Connell, Bellgrove, et al., 2009). Crucially, the early Pe was only generated for aware errors, unambiguously translating its sensitivity (like the ERN) to error awareness. This finding is in contrast with the study of O'Connell, Bellgrove, et al. (2009), in which an early Pe was observed to aware, unaware errors as well as correct responses. Furthermore, while it was not explicitly tested statistically, visual inspection of their data actually suggests a clearly larger early Pe to aware errors than to unaware errors and correct responses at more central sites, which indirectly corroborates the assumption that the early Pe is well sensitive to error awareness as well (following the ERN). In addition, because of the undisputed link in the literature between the late Pe and error awareness (Endrass et al., 2012; O'Connell et al., 2007), we expected a clear error awareness effect for this mid-latency response locked ERP component. In line with this prevailing view and previous neurophysiological research (Dhar et al., 2011; Endrass et al., 2007; O'Connell et al., 2007; Shalgi, Barkan, & Deouell, 2009) we found that the centro-parietal late Pe was only elicited in case of aware errors, but was not expressed for unaware errors (or hits).

More generally, because our new ERP results clearly show that error awareness influenced all three components (ERN, early and late Pe) following error commission concurrently, it appears more parsimonious to conclude that error awareness does not only depend on the late Pe, which has been the prevailing view for a long time in psychophysiology. In this context, our results suggest instead that error awareness should be best conceived as a (dynamic) accumulation of evidence process, where the late Pe might actually correspond to the last/final stage or end process (accumulating evidence account; Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010), with significant and earlier contributions of the ERN (and early Pe) to it as well. In this framework, several sources of error information successively become available over time and influence in turn whether an error will eventually be consciously detected or not. Consequently, dependent on whether (yes/no) and when (early/late) sources of error evidence are available after error commission, all error-related components can be

influenced and enhanced during the (progressive) emergence of error awareness. For example, interoceptive awareness, an internal source of information that presumably becomes available at late stages after error commission (Ullsperger et al., 2010), has been shown to specifically influence the amplitude of the late Pe, while visibility of the hand (external evidence) was of importance for sensitivity of the ERN to error awareness (Godefroid et al., 2016).

Changes in neurophysiological mechanisms of error awareness with ADHD

No group difference for the early awareness effect at the ERN level was observed between adults with and without ADHD. Although a meta-analysis on error monitoring in adult ADHD (Geburek et al., 2013) demonstrated attenuated ERN amplitudes in individuals with ADHD, it is important to note that this conclusion was based on studies that used tasks that did not titrate error awareness directly. Our new findings regarding the ERN are in line with O'Connell et al. (2009) and confirmed that ADHD does not compromise error awareness because of a selective change of the ERN component.

Noteworthy, the error awareness effect at the early Pe level was larger in typically developed adults than adults with ADHD, which is not compatible with the finding reported by O'Connell et al. (2009) showing a condition-unspecific lower Pe with ADHD. Although the early Pe and ERN showed similar sensitivity to error awareness and may share some common/generic monitoring mechanisms (Debener et al., 2005; Luu et al., 2004; Van Veen & Carter, 2002), yet, given the clearly different scalp topographies, neural generators and susceptibility to ADHD in the present case, we can conclude that they likely reflect successive but distinct stages of processing during error commission. As such, our new results are informative because previous ERP studies have typically neglected the role and function of the early Pe.

With respect to the possible modulation of the late Pe component by ADHD, we did not find a group difference however, thereby we failed to replicate the findings of O'Connell, Bellgrove, et al. (2009). Interestingly, we recently found interoceptive awareness to be spared in adults with ADHD (Godefroid & Wiersema, submitted), which fits with the current ERP result showing a normal error awareness-related late Pe in adults with ADHD. However, the question still arises whether some methodological factors might have impeded replicating the findings of O'Connell, Bellgrove, et al. (2009).

First, a different paradigm was used in this study. With our speeded Go/No-Go paradigm, a RT limit was imposed with the added value of a high amount of commission errors collected in a short time period. Moreover, an asset of our task was that this RT limit (that enforced error commission) was calculated and calibrated for each subject and trial separately, as opposed to the use of a fixed RT limit or response deadline. This way, error commission was eventually balanced between the two groups, which is an important pre-requisite when the aim is to compare error-related ERP effects between them, as the number of error trials included in the ERP averages necessarily influences the reliability of the ERP waveforms computed. Second, while the ADHD sample in the O'Connell et al. (2009) study included almost exclusively male participants, gender was balanced in our study. However, in our analyses, when we included gender as a covariate, we did not find evidence for differential behavioral or ERP effects with this variable. Third, as ADHD is a heterogeneous disorder, we have to acknowledge that our sample might not be completely representative of the disorder and replication can thus be challenging for different reasons. For example, different subgroups with distinct neuropsychological deficits or profiles may exist (Sonuga-Barke, 2003). In addition, we feel confident that our sample of adults with ADHD was not only large enough, but also sufficiently severe as a formal diagnosis by a specialist team was required for participation, and this diagnosis was verified with a diagnostic interview.

Complementary source localization results revealed that the reduced error awareness effect at the early Pe level in ADHD was related to both enhanced activation of the rIFG and decreased activity in the lS/MFG, compared to the control subjects. The S/MFG has previously been associated with error awareness, showing increased activation for aware compared to unaware errors (Hester et al., 2005) and is also part of the default mode network (Daniels et al., 2010), which tentatively suggests that the ADHD group may have been less internally focused during the meta-cognitive process of error awareness. Importantly, error awareness performance (i.e., the percentage of aware errors) was not associated with activation of the S/MFG, but was found to be specifically related to activation of the rIFG in the ADHD group, with more activation in this region going together with less error awareness. The rIFG, as a part of the central executive network (Daniels et al., 2010), has been consistently but not uniquely related to response inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Menon,

Adleman, White, Glover, & Reiss, 2001) and has been found disturbed in ADHD (Lei et al., 2015; van Rooij et al., 2015) with findings of both decreased (Rubia, 2011) and increased activation in the rIFG during response inhibition, as shown in a recent meta-analysis (Lei et al., 2015). The current findings might indicate that individuals with ADHD still (over)activate a brain region (rIFG) critically involved in response inhibition 200 ms after error commission (during the early Pe time interval), and that this effect may be related to diminished error awareness, even though we failed to find such a clear behavioral deficit in our study. Whether this is the expression of decreased error awareness per se or alternatively the alteration of (central) executive functions in ADHD that contribute to it remains an open question, and requires therefore additional experimentation.

Implications

Our new ERP findings have important implications for the conceptualization of error awareness and for further research. The observation that in addition to the late Pe, both the ERN and the early Pe were sensitive to error awareness suggests that the current dichotomy between unconscious and conscious processing of errors, as likely reflected by the ERN and late Pe respectively, is probably artificial and too simplistic. Rather, how conscious processing is reflected in the error processing components seems to be dependent on several methodological factors, such as the experimental paradigm used (Wessel, 2012). Further research is warranted to gain a better insight into the actual function of the early Pe, as our new results for this ERP component unequivocally demonstrate that it is a distinct component compared to the preceding ERN and subsequent late Pe (Arbel & Donchin, 2009; Endrass et al., 2012), and moreover it seems to be selectively impaired in ADHD (unlike these two other error-related activities that flanked it). Further, the actual contribution of the late Pe to error awareness probably needs some reconsideration, as our results suggest that it is not the exclusive correlate of error awareness. The late Pe has recently been argued to reflect decision confidence instead (Boldt & Yeung, 2015). Related to this notion, it is currently not entirely clear though how an intact ERN and an impaired early Pe in ADHD can be observed together with a normal late Pe, when a putative accumulation of evidence process fostering the conscious appraisal of error making is postulated to account for these (three) neurophysiological effects taking place at the ERN, early Pe and late Pe levels.

Speculatively at this stage, it could be suggested that in case of ADHD, the accumulation of error evidence is more noisy or blurry (early Pe) but despite of this, individuals are equally confident about making an error as typically developed controls. Further research including confidence ratings (metacognition) is needed to corroborate this intriguing possibility at the empirical level. In addition, notwithstanding the inconsistent findings in literature and despite the lack of behavioral impairments in our study, findings generally suggest error awareness deficits in ADHD, and further research is therefore warranted to discover which sources of error evidence may be wrongly interpreted or addressed in ADHD to eventually better understand the self-regulatory problems characterizing this patient group.

Conclusion

The present ERP study clarifies and extends the nature and extent of error awareness deficits in adult ADHD, as evidenced using scalp ERP methods and a standard Go/No-Go task including a (secondary) error verification task. While error awareness reliably influenced the magnitude of three ERP components of interest (ERN, early Pe and late Pe), ADHD selectively influenced the early Pe during error awareness, without any repercussion at the behavioral level however, given the specifics of the speeded go/nogo task used in this study. As such, our ERP results cast doubt on the prevailing view that the late Pe is the electrophysiological correlate of error awareness. Moreover, the selective amplitude reduction of the early Pe in ADHD when detecting consciously unwanted response errors was accompanied by an increased activation of the rIFG but decreased activation of the lS/MFG. Interestingly, the amplitude of the rIFG was negatively associated with the percentage of aware errors in the ADHD group, suggesting a link between this region and the mental process enabling errors to reach awareness rapidly following their inadvertent onset. More generally, our findings emphasize the importance of using an explicit error verification task (combined with ERP methods) to inform about the changes in error awareness processes arising as a function of ADHD.

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CHAPTER 5

IMPAIRED PROCESSING OF TASK-IRRELEVANT SALIENT INFORMATION IN ADULTS WITH ADHD: EVIDENCE FROM EVENT-RELATED POTENTIALS[1]

ABSTRACT

The current study examined the mechanisms of attention allocation in adult ADHD to investigate the frequently reported diminished target processing in ADHD as well as the less consistently observed increased distractibility by task-irrelevant distracting stimuli. To this end, while high-density EEG was recorded, 25 adults with ADHD and 23 healthy controls completed a four-stimulus oddball task that comprised a frequently presented standard stimulus and three different categories of equally infrequent stimuli: task-relevant targets, task-irrelevant non-targets, and task-irrelevant unfamiliar novels. By applying specific contrasts, this allowed us to disentangle pure effects of three kinds of salience, namely targetness (targets vs. non-targets), deviance (non-targets vs. standards) and novelty (novels vs. non-targets). Distinct effects of targetness, deviance and novelty across several components were found. At the behavioral level, no group differences between adults with and without ADHD were observed. Irrespective of type of salience, a marginally significantly smaller P2 amplitude in the ADHD group was observed, suggestive of a general stimulus identification deficit or disturbed early pre-conscious attentional processing in ADHD. Contrary to our expectations, no difference between groups was found for the P3b amplitude to targets or the novelty P3 to non-targets and novels, however in adults with ADHD a clear P3b to novels was apparent, which was absent in controls. This latter finding indicates deficient attention allocation in adults with ADHD, more specifically increased sustained processing of task-irrelevant novel events.

[1] Based on Godefroid, E., & Wiersema, J. R. (revision submitted). Impaired processing of task-irrelevant salient information in adults with Attention Deficit Hyperactivity Disorder. *Journal of Abnormal Psychology*.

INTRODUCTION

With estimated prevalence rates ranging from 5 - 7% across the life span (Willcutt, 2012), to 3.4% in childhood and adolescence (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015) and circa 3% in adulthood (Matte et al., 2015; Moffitt et al., 2015), *Attention-Deficit/Hyperactivity Disorder* (*ADHD*) is one of the most common neurodevelopmental disorders. ADHD is characterized by attention problems and/or hyperactive/ impulsive behavior leading to impairments in social, school or work settings (*DSM-5*; American Psychiatric Association, [APA] 2013). Attention problems present themselves in daily life as difficulties maintaining focus on the task at hand and being easily distracted by external stimuli. The exact mechanisms underlying these difficulties are however not known.

Attention can be either allocated voluntarily by instruction or involuntarily drawn by distracting stimuli. Both types of attention allocation have been extensively studied by means of the oddball paradigm and event-related potentials (ERPs). In the two-stimulus oddball task, an infrequently repeated task-relevant target stimulus to which participants are instructed to respond is presented in a sequence of frequently repeated task-irrelevant standard stimuli. It has repeatedly been shown that this target evokes the classical P3, namely the *P3b*, a positive peak between 300 and 600 ms after stimulus onset at parietal sites (Polich, 2007). The amplitude of the P3b is associated with working memory context updating, indexes the amount of attentional resources allocated to a stimulus (Kok, 2001), and reflects top-down attention to task-relevant events. In the three-stimulus variant of the oddball task, besides frequent standards and an infrequent task-relevant target, an equally infrequent but behaviorally irrelevant novel stimulus is presented. This novel also elicits a variant of the P3, called the *novelty P3*, which is a more (fronto-)centrally distributed positive deflection evoked between 300 and 400 ms after stimulus onset (Friedman, Cycowicz, & Gaeta, 2001). The novelty P3 reflects the bottom-up reallocation of attention to distracting stimuli and is deemed the neural correlate of the orienting response (Friedman et al., 2001; Polich, 2007).

There is ample evidence for inefficient attention allocation to task-relevant target stimuli in ADHD. A smaller P3b is consistently observed in children (review: Johnstone, Barry, & Clarke, 2013) as well as in adults with ADHD (meta-analysis: Szuromi, Czobor,

Komlósi, & Bitter, 2011). Moreover, reduced neural activity during target processing has been observed in fMRI studies in both auditory and visual oddball tasks (Rubia, Smith, Brammer, & Taylor, 2007; Stevens, Pearlson, & Kiehl, 2007; Tamm, Menon, & Reiss, 2006). In contrast, findings with regard to the processing of distracting novels in ADHD are inconclusive. In children with ADHD, the novelty P3 amplitude to novels has been found either enhanced (visual discrimination task: Gumenyuk et al., 2005; visual two-choice discrimination task: van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007), or unaltered (irrelevant-probe paradigm: Jonkman et al., 2000). In an fMRI study, children and adolescents with ADHD were found to show reduced neural activity to auditory novels (Stevens et al., 2007). Research on the novelty P3 in adults with ADHD is scarce. To our knowledge, only one study has reported on the novelty P3 in adults with ADHD (see below: Marzinzik et al., 2012). Strikingly, novels do not always seem to worsen performance in ADHD as two studies observed better performance in ADHD after presentation of novels which is suggestive of a beneficial effect of novels in certain situations for this patient group (Tegelbeckers et al., 2016; van Mourik et al., 2007). To date, it is thus not yet clear whether deficient attention allocation in ADHD is solely related to decreased processing of task-relevant stimuli such as targets or whether and how much it incorporates increased distraction by task-irrelevant stimuli, such as novels, as well. In addition, research on novelty processing in adults with ADHD is very scarce.

The inconsistent results across studies on novelty processing in ADHD may relate to the conceptualization of the novel that differs greatly across studies (i.e., repeated or unique). According to Zaehle et al. (2013), real novels are unique on each occurrence and encountered for the first time, while deviant stimuli (non-targets), are merely familiar repeated stimuli with a low probability. In some cases, reported findings could therefore actually reflect deviance effects instead of pure novelty effects. Two studies so far have explicitly attempted to disentangle the processing of novels from non-targets in individuals with ADHD. These studies used a modified four-stimulus oddball task. A recent fMRI study (Tegelbeckers et al., 2015) found that children with ADHD compared to typically developing children did not show neural deactivation in frontal and temporal areas in response to novels and showed enhanced neural activity in novelty-related regions to non-targets. Surprisingly, groups did not differ for target processing. An ERP study (Marzinzik et al., 2012) reported a decreased P3b to targets in adults with ADHD,

together with typical neural responses to deviants. They further contrasted novels that were rated afterwards as meaningful and as meaningless novels, and found that the novelty P3 amplitude for meaningless compared to meaningful novels was enhanced in healthy controls, while it did not differentiate between types of novels in adults with ADHD, while the reverse was found for the P3b in response to novels, where only adults with ADHD showed increased sustained processing of meaningful novels. That novels may elicit a P3b (be it smaller than for targets) is in accord with previous observations (e.g., Delplanque, Silvert, Hot, & Sequeira, 2005; Tenke, Kayser, Stewart, & Bruder, 2010) and may indicate sustained processing of novels as if they are task-relevant. The findings seem thus to suggest, as the authors also argue, a dysfunction of stimulus weighing in ADHD, reflected in enhanced sustained processing of salient task-irrelevant information. All together, these findings clearly suggest deficient attention allocation in ADHD and recent results point to abnormal salience attribution of novel information in this condition. Still, studies are scarce and novels used in different studies differ greatly according to their familiarity to the subject, their visual complexity and on whether a meaning can be associated with them. The present study therefore tried to more strictly investigate the processing of deviant and novel stimuli in adults with ADHD by controlling for these potentially confounding factors.

In addition, we will also evaluate other ERP components that have been associated with novelty processing. According to some authors, the N2 is a more genuine reflection of novelty, while the novelty P3 is actually a reflection of deviance (Schomaker & Meeter, 2015). Furthermore, sensitivity to novelty has also been reported for the P2, which precedes the N2 (Daffner, Alperin, Mott, Tusch, & Holcomb, 2015; Riis et al., 2009). Mixed results regarding alterations in the amplitudes of these components to targets and novels in children with ADHD have been reported, while the evidence in adult ADHD is scarce (Barry, Johnstone, & Clarke, 2003; Barry et al., 2009; Johnstone et al., 2013; Oades, 1998; Prox, Dietrich, Zhang, Emrich, & Ohlmeier, 2007; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006; Wild-Wall, Oades, Schmidt-Wessels, Christiansen, & Falkenstein, 2009; Woltering, Liu, Rokeach, & Tannock, 2013). Furthermore, as already mentioned, the P3b may also be elicited for novels, which is suggestive of the novel sometimes being further processed as if task-relevant, probably since a novel might be a potentially behaviorally important stimulus. Chong et al. (2008)

showed that novelty processing may continue after the P3b, reflected in a frontally distributed late positive slow wave activity.

We applied a four-stimulus oddball task in which visually simple stimuli were used. Novels were unfamiliar, unique on each occurrence and were not associated with meaning. In line with Zaehle et al. (2013), to disentangle the pure effects of different types of salience, specific contrasts were performed, namely targetness (targets vs. non-targets), deviance (non-targets vs. standards), and novelty (novels vs. non-targets). All other contrasts are more difficult to interpret because these conditions differ in more than one dimension. For example, standards are frequent and familiar, while novels are infrequent and unfamiliar and the contrast between novels and standards would therefore not be a pure reflection of novelty.

In line with previous studies, we predicted slower responding and smaller P3b amplitudes to targets in ADHD. Findings so far regarding the novelty P3 in ADHD have been inconsistent. If ADHD is indeed characterized by an increased distractibility by task-irrelevant salient stimuli, we might expect to see enhanced novelty P3 amplitudes to novels (and non-targets) in adults with ADHD. We further expected to observe sustained processing of novels in ADHD, more so than in controls, as reflected by a larger P3b to novels. Based on the scarce literature, no a priori predictions regarding the P2 and N2 were formulated.

METHOD

Participants

Twenty-five adults with ADHD (mean age: *M*(*SD*) = 24.04 (*5.26*), 13 males, one left-handed) participated in the study. The control group consisted of 23 typically developed adults (mean age: *M*(*SD*) = 23.57 (*3.17*), 13 males, four left-handed), matched on age ($F(1, 47) = 0.14$, $p = .710$) and sex ($\chi^2(1) = 0.10$, $p = .753$). IQ was slightly higher for controls ($F(1, 47) = 4.45$, $p = .040$; see Table 1).

Individuals with ADHD were recruited through staff members, advertisements, self-support groups for ADHD, and a local database (adults with ADHD who participated in previous research). All adults with ADHD had a formal diagnosis established by a team

with a psychiatrist involved before entering the study. A semi-structured clinical interview was used to to confirm diagnosis (DIVA; Diagnostisch Interview Voor ADHD bij Volwassenen 2.0, Kooij & Francken, 2010). For confirmation of a diagnosis in childhood and adulthood, respectively six or four, out of nine DSM-criteria of inattention and/or hyperactivity and impulsivity must have been met. Medication use was interrupted 48 hr prior to participation in the experiment. Eight adults with ADHD were currently taking medication, while four participants had never taken medication. Thirteen participants occasionally took medication during exam periods or important work-related projects. Control participants were recruited through an online database and advertisements. Exclusion criteria for all participants were an estimated IQ below 80, history of brain-related illness or neurological disorder and a clinical diagnosis of depression or autism spectrum disorder. Comorbid diagnoses in the adult ADHD group included anxiety disorder (n = 1), dyslexia (n = 4), dysgraphia (n = 1) and dyscalculia (n = 4). Control participants were not included in the study if they exhibited four or more symptoms in the attentive or hyperactive/impulsive domain, as evaluated by the Zelfrapportage Vragenlijst voor Aandachtsproblemen en Hyperactiviteit (ZVAH; Kooij et al., 2010), gauging presence of childhood or adulthood ADHD.

Both groups completed an abbreviated version (Meyers, Zellinger, Kockler, Wagner, & Miller, 2013) of the WAIS-IV (Wechsler Adult Intelligence Scale-IV; Wechsler, 2008), except for the individuals with ADHD who were recruited through the local database since they had already completed the same abbreviated version (Ryan & Ward, 1999) of the WAIS-III (Wechsler, 1997) in a previous study. Not surprisingly, the adult ADHD group scored significantly higher on the WURS (Wender Utah Rating Scale; Wender, Ward, & Reimherr, 1993), a measure of presence of childhood ADHD, ($F(1, 47) = 110.69$, $p < .001$) and on the DSM oriented ADHD scale of the ASR (Adult Self-Report; Achenbach & Rescorla, 2003) than the control group ($F(1, 47) = 44.90$, $p < .001$). No difference in substance abuse (DSM oriented scale of the ASR) was observed ($F(1, 47) = 0.69$, $p = .412$), but the ADHD group scored significantly higher on the DSM oriented depression scale ($F(1, 47) = 13.99$, $p = .001$), and marginally significantly higher on the anxiety scale ($F(1, 47) = 3.70$, $p = 0.061$). Sample characteristics are reported in Table1.

Table 1. Sample characteristics

	ADHD	Control
IQ	103.72 (12.86)	111.35 (12.12)
DIVA: ADHD C/I	16/9	-
WURS	51.36 (14.04)	16.65 (7.58)
ASR		
ADHD	74.64 (11.90)	55.74 (6.70)
Substance abuse	57.60 (6.51)	56.00 (6.89)
Anxiety	56.24 (6.23)	53.09 (4.99)
Depression	60.40 (9.22)	52.70 (3.67)

Note. Values are shown as means (*SD*). IQ = measured with *Wechsler Preschool and Primary Scale of Intelligence – Fourth edition*, DIVA = *Diagnostisch Interview voor ADHD bij Volwassenen* 2.0, C = combined subtype, I = inattentive subtype, WURS = *Wender Utah Rating Scale,* ASR = *Adult Self-Report*.

Four-stimulus oddball task

In the task (Figure 1) black outline figures were sequentially presented, foveally on a white background. This sequence of stimuli comprised one frequently presented standard stimulus (i.e., square, 70%), an infrequent task-relevant target stimulus (i.e., circle, 10%), an infrequent task-irrelevant non-target stimulus (i.e., triangle, 10%), and an infrequent task-irrelevant novel stimulus (10%) that changed identity on every occurrence. These novels were meaningless and unfamiliar figures. Participants were instructed to respond as accurately and rapidly as possible to targets by means of a button press on the response box with the index finger of their dominant hand and withhold responding to other stimuli.

The stimuli were pseudo-randomly presented, with the restriction that two infrequent stimuli (target, non-target or novel) could not follow each other, such that they were always preceded by at least two standards. The variable amount of preceding standards was equally balanced across the infrequent stimuli. Each trial started with the presentation of a stimulus from one of the four stimulus categories for 200 ms, followed by a white blank screen which was presented for 1800 ms. Before the presentation of the next stimulus, a delay was randomly presented between 0 and 400 ms during which the blank screen was presented anew, precluding the anticipation of the next stimulus.

A total of 400 stimuli was presented (280 standards, 40 targets, 40 non-targets, 40 novels), divided over two blocks. A short break was introduced between two consecutive blocks. The total duration of the task was about 15 minutes. Ten practice trials (containing one target, one non-target, and a novel not used in the main task) were administered at the beginning of the experiment.

After completion of the four-stimulus oddball task, participants were asked to rate whether a meaning could be associated with the novels presented during the main task. For every novel, participants had to respond with a yes/no-answer. Novels that were associated with meaning on the individual participant level were excluded from further analyses. The number of novels rated as associated with meaning did not differ between groups (ADHD: *M*(*SD*) = 13.00 (*7.75*), control: *M*(*SD*) = 9.13 (*7.82*), $F(1, 47) = 2.96$, $p = .092$).

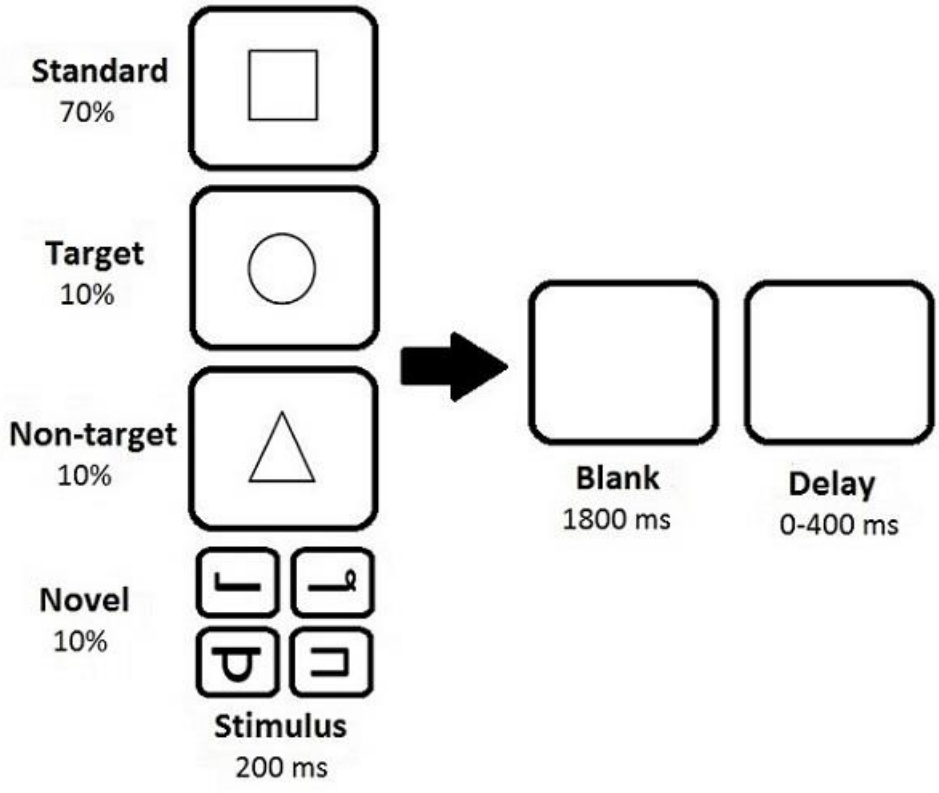

Figure 2. Four-stimulus oddball task. A stimulus from one of the four stimulus categories (standard, target, non-target, novel) was presented for 200 ms. This stimulus was followed by a blank screen, presented for 1800 ms, and a random delay (0-400 ms). For illustrative purposes, four different novels are presented.

Procedure

The task was programmed using E-Prime 2.0 software (http://www.pstnet.com/products/e-prime/) and presented on a 19-inch CRT monitor with 640x480 screen resolution and a 60Hz refresh rate. Participants were seated in a sound-attenuated, dimly lit and electrically shielded room, sitting approximately 60 cm in front of the computer screen. Each participant signed an informed consent prior to participation in the experiment and was financially reimbursed for their participation in the experiment. The study was approved by the local ethics committee of the Faculty of Psychological and Educational Sciences, Ghent University.

The study was part of a larger experimental set-up. The oddball task was administered together with other behavioral tasks; results of these tasks will be reported elsewhere. The order of the tasks was counterbalanced. Verbal as well as written instructions were given prior to the start of each task.

EEG acquisition and data reduction

Electroencephalogram (EEG) was continuously recorded at a sampling rate of 1024 Hz with a 128-channel Biosemi ActiveTwo system (Biosemi, Amsterdam, The Netherlands). The signal was referenced online to a CMS-DRL ground. Vertical EEG was recorded from infraorbital and supraorbital electrodes placed in line with the pupil of the right eye, while horizontal EEG was acquired through electrodes positioned on the outer cantus of each eye. Data were recalculated offline against the average reference and down-sampled to 512 Hz sampling rate. A low pass filter of 80 Hz, a high pass filter of 0.25 Hz and 50 Hz Notch filter were applied. The signal was corrected for blinks (Gratton, Coles, & Donchin, 1983). ERPs of interest were computed offline with Brain Vision Analyzer 2.0 (Brain Products, GmbH, Munich, Germany). Segmentation was performed relative to stimulus onset (-200 to 1000 ms). A pre-stimulus baseline (-200 to 0 ms) was applied to each segment. Artifacts were semi-automatically detected and rejected with a ± 100 μV criterion relative to baseline. Noisy electrodes were interpolated using a spherical spline procedure (order of spline = 4). Finally, a 30 Hz low-pass filter was applied on the individual averaged data after analyses for smoothing purposes. Grand average waveforms were computed separately for the four conditions (standards, targets, non-targets, novels).

Data analysis

Performance. Reaction times faster than 150 ms and exceeding 1500 ms were removed from the analyses. Target SD-RT was calculated as the average standard deviation of the target RT per participant. Very few omission errors to targets (less than 0.73%) and commission errors to standards, non-targets or novels (less than 0.16%) were made. These variables were therefore not further analyzed. Two-tailed independent samples *t*-tests were performed to compare groups on performance data.

Electrophysiological measures. A P2 and N2 were elicited at fronto-central sites. At central sites, a novelty P3 was observed, followed by a P3b which was evoked centro-parietally. As expected, at frontal sites, a positive-going slow wave was observed for novels. In addition, in line with the study of Chong et al. (2008), also a negative-going slow wave to targets was observed. Based on the obvious topographical properties of the data, the peak amplitudes of the P2 and N2 were calculated between 140 and 240 ms and 265 and 335 ms, respectively, at Fz and FCz, and the mean amplitude of the novelty P3 was calculated between 380 and 450 ms at Cz following stimulus presentation. The mean amplitude of the P3b at Pz was calculated between 380 and 500 ms following stimulus presentation (Figure 2). As the slow waves for targets and novels were broad sustained components, mean amplitudes were exported. Mean amplitudes for the positive-going slow wave for novels was calculated at Fpz between 500 and 900 ms and for the negative-going slow wave for targets at AFz and Fz between 400 and 800 ms. Visual inspection of the data suggested a difference between groups for the slow wave for targets between 800 and 1000 ms. Mean amplitudes of the slow wave for targets were therefore also calculated between 800 and 1000 ms at AFz and Fz (Figure 4) as an additional exploratory analysis. For the analyses on slow waves, data of one participant were excluded as relevant electrodes were contaminated by too many artefacts.

In line with the study of Zaehle et al. (2013), the nature of our paradigm allowed us to make direct comparisons to test for pure effects of different types of salience: deviance (non-targets vs. standards), targetness (targets vs. non-targets) and novelty (novels vs. non-targets). Mixed ANOVAs were performed with within-subject factors type of salience (i.e., deviance: non-targets vs. standards; targetness: targets vs. non-

targets; novelty: novel vs. non-targets) and between-subjects factor group (ADHD vs. control) on the amplitude values of each component of interest, with an additional within-subjects factor electrode for the P2 and N2 (2 levels: Fz, FCz) and the negative-going slow wave to targets (2 levels: AFz, Fz).

When sphericity assumptions were violated as indicated by a Mauchly test, Greenhouse-Geisser corrections were used. If a type of salience by group interaction was apparent, amplitude values were collapsed across electrodes (provided that no three-way interaction type of salience by group by electrode was observed) for further analyses. In addition, if a type of salience by group interaction was apparent, paired samples *t*-tests were applied per group to compare the effects of targetness, deviance and novelty on the collapsed values.

RESULTS

Behavioral data

Behavioral data for RT and accuracy are reported in Table 2, separately for the two groups. Groups did not differ on target RT ($t(46) = 1.00$, $p = .324$, $d = 0.29$), or target SD-RT ($t(46) = 1.59$, $p = .119$, $d = 0.46$).

Table 2. Behavioral data of the four-stimulus oddball task for the ADHD and control group

	ADHD	Control
Target RT	396.16 (70.07)	379.72 (38.22)
Target SD-RT	91.81 (41.62)	74.96 (30.59)
Percentage omission errors (target)	1.40 (2.05)	0.00 (0.00)
Percentage commission errors (standard + non-target + novel)	0.20 (0.25)	0.12 (0.22)

Note. Values are shown as means (*SD*).

Electrophysiological measures

P2. The main effect of deviance (F(1, 46) = 10.17, p = .003, η^2_p = .18) reached significance, with larger P2 amplitudes for non-targets than for standards. The main effect of group was marginally significant (F(1, 46) = 3.52, p = .067, η^2_p = .07), with a larger P2 amplitude in the control group relative to the ADHD group. The main effect of electrode (F(1, 46) = 4.24, p = .045, η^2_p = .08) and the interaction between deviance and electrode (F(1, 46) = 6.36, p = .015, η^2_p = .12) was also significant; the P2 amplitude was larger at FCz than Fz, while the deviance effect was smaller at FCz (p = .028, d = 0.32) than at Fz (p = .001, d = 0.57).

For the ANOVAs on targetness and novelty, the main effects of targetness (F(1, 46) = 10.72, p = .002, η^2_p = .19) and novelty reached significance (F(1, 46) = 8.96, p = .004, η^2_p = .16). The P2 amplitude for non-targets was smaller than for targets and novels. For the ANOVA on novelty, there was a marginally significant main effect of group (F(1, 46) = 3.59, p = .064, η^2_p = .07), showing larger P2 amplitudes for the control group compared to the ADHD group. All other main effects and two-way or three-way interactions were not significant (all p's > .125).

N2. The main effects of deviance (F(1, 46) = 44.11, p < .001, η^2_p = .49) and novelty (F(1, 46) = 10.55, p = .002, η^2_p = .19) reached significance, while the main effect of targetness (F(1, 46) = 3.65, p = .062, η^2_p = .07) was marginally significant. The N2 amplitude for non-targets was larger than for standards, while it was smaller than for targets and novels.

The main effects of electrode reached significance for the ANOVAs on deviance (F(1, 46) = 26.92, p < .001, η^2_p = .37) and novelty (F(1, 46) = 6.26, p = .016, η^2_p = .12). A larger N2 amplitude was observed at Fz compared to FCz. The interaction between targetness and electrode (F(1, 46) = 7.88, p = .007, η^2_p = .15) also reached significance, while the interaction between novelty and electrode was marginally significant (F(1, 46) = 3.76, p = .059, η^2_p = .08). The targetness effect was not significant at Fz (p = .798, d = 0.04), while it was significant at FCz (p = .004, d = 0.49). The novelty effect was smaller at Fz (p = .036, d = 0.33) than at FCz (p < .001, d = 0.53). All other main effects and all other two-way interaction or three-way interactions did not reach significance (all p's > .113).

Novelty P3. The main effect of deviance ($F(1, 46) = 5.56$, $p = .023$, $\eta^2_p = .11$) and targetness ($F(1, 46) = 17.00$, $p < .001$, $\eta^2_p = .27$) reached significance. The novelty P3 amplitude for non-targets was larger than for standards, while the novelty P3 amplitude was larger for targets than for non-targets. All other main effects or two-way interactions did not reach significance (all *p*'s > .144).

Visual inspection of the data suggested a difference between groups for the novelty P3 at Fz. This could however not be confirmed by additional exploratory analyses on the novelty P3 at Fz; only a significant main effect of deviance ($F(1, 46) = 7.64$, $p = .008$, $\eta^2_p = .14$) and a marginally significant main effect of targetness ($F(1, 46) = 3.34$, $p = .074$, $\eta^2_p = .07$) were observed, with the novelty P3 being smaller for non-targets than for standards, and larger for non-targets than for targets.

P3b. The main effects of deviance ($F(1, 46) = 16.56$, $p < .001$, $\eta^2_p = .27$) and targetness ($F(1, 46) = 114.61$, $p < .001$, $\eta^2_p = .71$) were significant. The P3b amplitude to non-targets was larger than to standards, while the P3b amplitude to targets was larger than to non-targets. A significant interaction between novelty and group was apparent ($F(1, 46) = 4.09$, $p = .049$, $\eta^2_p = .08$). Paired samples *t*-tests showed that the novelty effect in the ADHD group was significant ($t(24) = 2.61$, $p = .015$, $d = 0.67$), while it was not in controls ($t(22) = -0.38$, $p = .706$, $d = 0.09$). All other main effects or two-way interactions did not reach significance (all *p*'s > .146, see Figure 2 and 3).

Slow wave to novels. The main effects of targetness ($F(1, 45) = 32.52$, $p < .001$, $\eta^2_p = .42$) and novelty ($F(1, 45) = 35.82$, $p < .001$, $\eta^2_p = .44$) were significant. The slow wave for novels was more positive-going than for non-targets, while this slow wave was more negative-going for targets than for non-targets. No other main effects or interactions reached significance (all *p*'s > .111, see Figure 4).

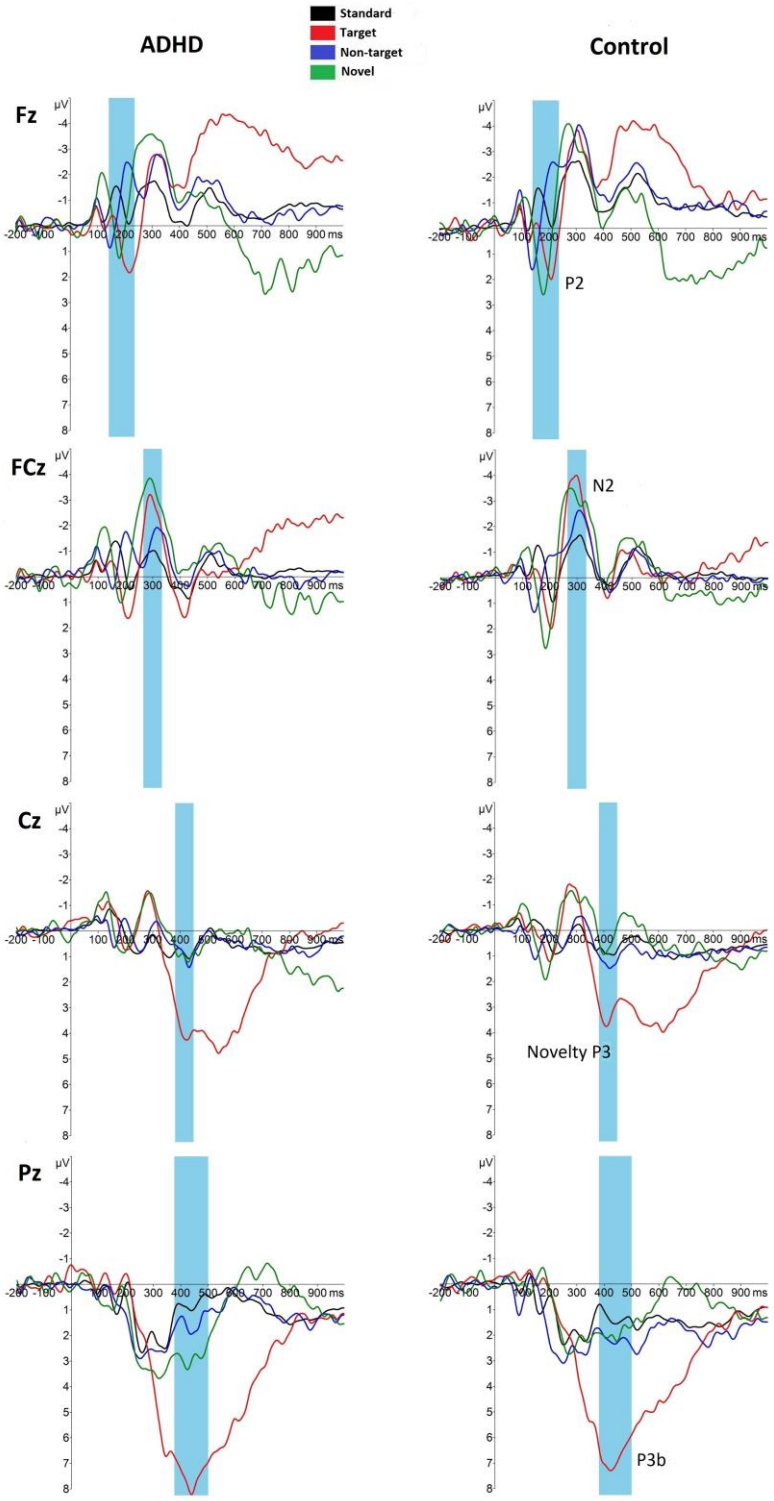

Figure 2. Grand average stimulus-locked ERP waveforms depicting P2, N2, novelty P3 and P3b at Fz, FCz, Cz and Pz for standards, targets, non-targets and novels, separately for the ADHD and control group.

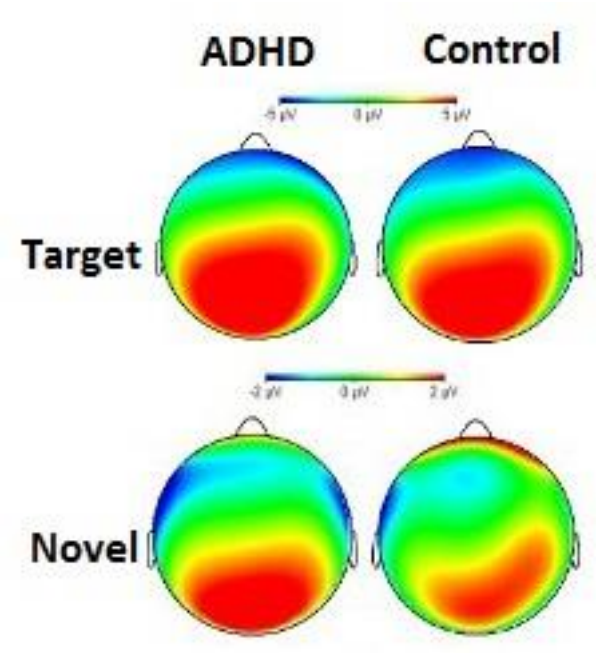

Figure 3. Topographical maps corresponding to the time window of the P3b (380-500 ms) for targets and novels.

Slow wave to targets. The main effects of targetness (F(1, 45) = 28.67, p < .001, η^2_p = .39) and novelty (F(1, 45) = 27.17, p < .001, η^2_p = .38) reached significance. This slow wave was more negative-going for targets than for non-targets, and more positive-going for novels than non-targets. For the ANOVAs on targetness and novelty, the interactions between targetness and electrode (F(1, 45) = 11.27, p = .002, η^2_p = .20) and between novelty and electrode (F(1, 45) = 33.58, p < .001, η^2_p = .30) were also significant. The targetness effect was significant at both electrode sites, but was larger at AFz (p < .001, d = 1.14) than Fz (p < .001, d = 0.77). The novelty effect was also significant at both electrode sites, but was also larger at AFz (p < .001, d = 1.09) than Fz (p < .001, d = 0.73). For the ANOVA on deviance, the main effect of electrode reached significance (F(1, 45) = 12.74, p =.001, η^2_p = .22). More negative amplitudes were observed at Fz than AFz. All other main effects or two-way interactions did not reach significance (all p's > .110).

Visual inspection of the data suggested a difference between groups for the slow wave for targets between 800 and 1000 ms. Additional exploratory analyses on the slow wave for targets between 800 and 1000 ms could however not confirm this. For targetness, the main effect electrode reached significance (F(1, 45) = 5.81, p = .020, η^2_p = .11). More negative amplitudes were observed at Fz than AFz. For novelty, the main

effects of novelty ($F(1, 45) = 38.04$, $p < .001$, $\eta^2_p = .46$) as well as electrode ($F(1, 45) = 17.19$, $p < .001$, $\eta^2_p = .28$) were significant. The slow wave for novels was more positive-going than for non-targets. More positive amplitudes were observed at AFz than Fz. The interaction between novelty and electrode also reached significance ($F(1, 45) = 9.11$, $p = .004$, $\eta^2_p = .17$). The novelty effect was also significant at both electrode sites, but was larger at AFz ($p < .001$, $d = 1.14$) than Fz ($p < .001$, $d = 1.08$). All other main effects or interactions did not reach significance (all p's > .103, see Figure 4).

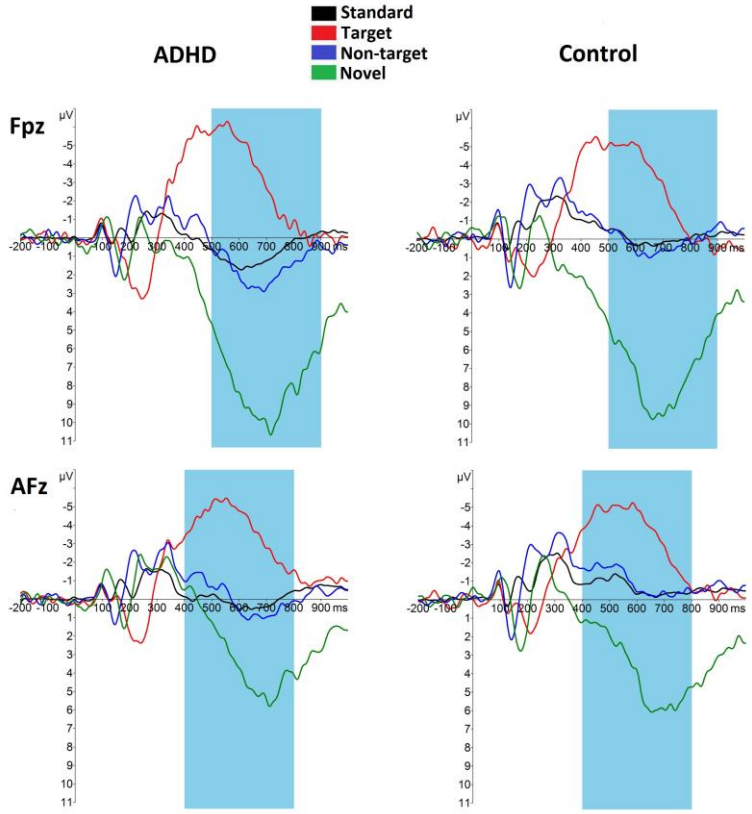

Figure 4. Grand average stimulus-locked ERP waveforms depicting the positive-going slow wave for novels and the positive-going slow wave for targets, separately for the ADHD and control group.

DISCUSSION

Our aim was to investigate the mechanisms of deficient attention allocation in ADHD by systematically disentangling the specific effects of different kinds of salience (i.e., targetness, deviance, novelty). To this end, high-density EEG was recorded, while participants performed a four-stimulus oddball task in which targets, deviant non-targets and novels with a unique identity on each occurrence were equally infrequently presented amongst frequent standards. Targetness influenced the P2, N2, novelty P3, P3b components and the slow wave to targets. Effects of deviance were observed for the P2, N2, novelty P3 and P3b components, while a main effect of novelty was apparent for the P2 and N2 components and the slow wave to novels. At the behavioral level, no group differences between adults with and without ADHD were observed. Against predictions, groups did not differ on the P3b amplitude to targets or the novelty P3 amplitude to non-targets or novels. However, as hypothesized, adults with ADHD showed larger P3b amplitudes to novels than controls, which suggests that individuals with ADHD have more difficulties to distinguish task-relevant and task-irrelevant novel stimuli, leading to sustained processing of task-irrelevant information. Furthermore, the findings seem to be supportive of deficiencies in early attentional mechanisms in ADHD, as a marginally significantly smaller P2 was observed, irrespective of type of stimulus.

Targetness, deviance and novelty

P2. The P2 is thought to reflect the inhibition of sensory input from further processing via automatic stimulus identification and discrimination/classification (Hegerl & Juckel, 1993) or inhibition of other channels of information competing for attention and further processing (Oades, 1998). The P2 component was modulated by targetness, deviance and novelty, which is in accord with recent research showing that this component also indexes motivational salience as determined by either task relevance or novelty (Daffner, Alperin, Mott, Tusch, & Holcomb, 2015; Riis et al., 2009). We give nuance to this observation by showing that the amplitude of the P2 component is also sensitive to another type of salience (i.e. deviance), which tentatively suggests that the P2 is a general marker of stimulus salience.

N2. The N2 component has been related to stimulus discrimination and is believed to represent an endogenous mismatch detection process (Näätänen & Picton, 1986). The visual N2 in particular is thought to be an index of stimulus unfamiliarity and sensitive to the deviation of a presented stimulus from stored representations (Daffner et al., 2000) or to signal a violation of expectancy (Wessel, Danielmeier, Morton, & Ullsperger, 2012). It is furthermore thought to represent a robust index of novelty (Schomaker & Meeter, 2015). Interestingly, the N2 similarly to the P2 was sensitive to novelty (while the novelty P3 was not, see below), since an added effect of novelty over deviance was observed. However, the P2 and N2 do not seem to specifically reflect novelty as effects of deviance and targetness were observed as well.

Novelty P3. As mentioned above, the novelty P3 reflects the bottom-up reallocation of attention to distracting stimuli and is deemed the neural correlate of the orienting response (Friedman et al., 2001; Polich, 2007). Unexpectedly, we found no significant effect of novelty on the novelty P3, but effects of deviance were found. This is in accord with the idea that the novelty P3 is not a genuine reflection of novelty, but rather reflects deviance processing (Schomaker & Meeter, 2015). In addition, the effect of targetness on the novelty P3 was significant. Previous studies have also reported a P3a to targets in an oddball task, dependent on the degree of target deviancy from background events. This P3a has been shown to be very similar to and potentially the same component as the novelty P3 (Knight, 1996; Simons, Graham, Miles, & Chen, 2001). Together with the findings on the P2 and N2 components, it seems to indicate that task-relevance already has an effect early on after stimulus onset, which continues with a P3b and slow wave to targets. As mentioned above, effects of task-relevance have previously been reported at the stage of the P2 component (Daffner et al., 2015; Riis et al., 2009).

P3b. Significant effects of deviance and targetness were observed for the P3b. With regard to the effect of targetness, the most consistent finding across studies is that targets elicit a P3b. The P3b is thought to reflect the context updating of working memory urged by the newly presented stimulus requiring an adaptation of the stimulus representation (Donchin & Coles, 1988) or is taken as an indicator of stimulus evaluation or top-down attentional resources allocated to a stimulus (Kok, 2001). The effect of deviance is therefore also in line with the working memory updating hypothesis of the

P3b in that deviant stimuli require an update of the stimulus representation. The fact that novelty did not show a main effect in the control group is probably due to the fact that novelty did not have an added effect over deviance. An exploratory contrast between novels and standards for the P3b amplitude was significant, which also implies updating of working memory after novels. Other accounts of the P3b have related it to context closure (Verleger, 1988) or event categorization (Kok, 2001).

Slow wave to novels. Positive slow waves are thought to reflect sustained stimulus processing after initial categorization (Ruchkin & Sutton, 1983; Ruchkin, Sutton, Kietzman & Silver, 1980). A clear frontally distributed positive-going slow wave was observed specifically for novels, in line with the study of Chong et al. (2008). This suggests sustained processing, specifically for novelty.

Slow wave to targets. In accord with the study of Chong et al. (2008), only for targets, a broad negative-going slow wave was observed, which most likely reflects working memory related operations (Ruchkin, Canoune, Johnson, & Ritter, 1995). This interpretation of the negative slow wave is plausible as it immediately follows the P3b which is taken to reflect sustained working memory updating (Donchin & Coles, 1988).

Attention allocation in ADHD

Although marginally significant, generally smaller P2 amplitudes were observed in the ADHD group compared to the control group, independent of the type of salience. With regard to the P2 component in ADHD, smaller as well as enlarged P2 amplitudes for the auditory and visual modalities (Barry, Johnstone, et al., 2003; Johnstone et al., 2013; Oades, 1998; Wiersema, van der Meere, Van Coster et al., 2006) have been observed in children with ADHD. Research regarding the P2 in adult ADHD is scarce. One ERP study found that the P2 to auditory targets was globally enhanced, while visual P2 amplitude was enlarged at the vertex in adults with ADHD compared to healthy controls in an inter-model auditory/visual oddball task (Barry et al., 2009). To our knowledge, this is the first study to report generally smaller P2 amplitudes in adult ADHD. According to Oades et al. (1996), smaller P2 amplitudes are reflective of an inhibitory process missing in the transition from exogenous to endogenous processing and may therefore relate to impulsive behavior. A study using an inter-model oddball task that found smaller

auditory P2 amplitudes to targets and smaller visual P2 amplitudes to non-targets in children with ADHD attributed this to a generalized stimulus identification deficit (Brown et al., 2005). These results suggest disturbed early automatic attentional processing in ADHD, irrespective of the type of salient stimulus.

The finding of an equally large P3b to targets for the ADHD and control group was quite surprising as a smaller P3b amplitude in ADHD is a robust finding in the literature on ADHD (Barry et al., 2003; Johnstone et al., 2013; Szuromi et al., 2011). However, interestingly, previous research with a four-stimulus oddball task in ADHD has found both deficient (ERP: Marzinzik et al., 2012) as well as intact target processing (fMRI: Tegelbeckers et al., 2015). This may suggest that the context in which task performance is measured in ADHD is important, which is in line with current thinking of ADHD as a highly context dependent disorder of self-regulation (Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010). The *state regulation deficit* (*SRD*) account (Sergeant, 2000; Sonuga-Barke et al., 2010; van der Meere, 2005) stresses that an optimal energetic (arousal/activation) state, which is influenced by contextual factors, is needed for good task performance and that individuals with ADHD have difficulty to optimally adjust their energetic state - to upregulate their underactivated state by allocating the necessary extra top-down attentional resources (effort) and are therefore not able to meet task demands. Interestingly, research along these lines has shown that whether or not the P3b amplitude to targets is smaller in ADHD depends on the presentation rate of stimuli, with smaller P3b amplitude in children and adults with ADHD only in slow paced (understimulated) conditions (Wiersema, van der Meere, Van Coster et al., 2006; Wiersema, van der Meere, Antrop, & Roeyers, 2006). Other studies have shown performance improvements in ADHD when external stimulation is provided by presenting white noise, probably elevating the arousal level (Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010; Söderlund, Sikström, & Smart, 2007), and importantly, after presentation of task-irrelevant novels (Tegelbeckers et al., 2016; van Mourik et al., 2007). Linking these findings to our study, it could be that the task design in the current study with several different stimuli, including novels and a relatively fast event rate was stimulating enough to keep the energetic level of individuals with ADHD at an optimal level. The possibility that a deficit in top-down allocation of attentional resources in

ADHD is state-dependent and may be counteracted by additional external stimulation provides an interesting avenue for future studies and clinical interventions.

Despite intact target processing, the findings did reveal a difference in salience attribution between groups. Groups did not differ on the novelty P3 for non-targets and novels, which is not in line with some studies showing an enhanced novelty P3 to novels in ADHD (Gumenyuk et al., 2005; Marzinzik et al., 2012; van Mourik et al., 2007). However, adults with ADHD showed sustained processing of novels at the stage of the P3b, which was not observed in controls. A P3b to novels has been previously observed (e.g., Delplanque et al., 2005; Tenke et al., 2010) and has also been observed altered in adults with ADHD (Marzinzik et al., 2012). As hypothesized, novels were thus perceived as and processed further as task-relevant stimuli by this patient group. In evolutionary terms, it is important to rapidly make a distinction between distracting stimuli that either do not need further processing and can be perceived as task-irrelevant or that do require an adequate behavioral response. Although the novels in our study were clearly task-irrelevant (i.e., did not require a behavioral response) and needed no further processing, adults with ADHD seem to be impaired in this process. Apparently, this sustained top-down processing of novels did not impair target processing, even though one may expect this extra top-down attention to novels to somehow affect top-down attention directed to targets. Further research should test whether this will be the case when greater demands are placed on top-down attentional resources, such as in tasks with higher task difficulty or tasks inducing non-optimal energetics state (e.g., slow event rate).

Implications

Our new ERP findings may have some important implications. First, our findings show that making a distinction between targetness, deviance and novelty by applying specific contrasts for pure effects of types of salience has added value for correct interpretation of findings and components. This way, in contrast to the general conception, we observed that both target and novelty processing occur at early and late stages of stimulus processing as effects of task-relevance and novelty were found in an early and late stage after stimulus onset, respectively. Interestingly, the P2 and N2 were sensitive to novelty (on top of deviance) while the novelty P3 was not. Second, our

findings are not supportive of a general (fixed) deficit of top-down attentional processing of task-relevant events in ADHD, but rather point to a disturbance in salience attribution to task-irrelevant novel events. If replicated in future studies, these findings may have a significant impact on treatment optimization.

Limitations

Some limitations have to be mentioned. First, as the novels used in our study were meaningless stimuli, we therefore do not know how meaningful novels would have influenced the data. In the study of Marzinzik et al. (2012), adults with ADHD showed more difficulties in processing meaningful than meaningless novels, which suggests that group differences in our study might have even been more pronounced in case of meaningful novels. Second, as we cannot generalize the results from our visual four-stimulus oddball task to other domains, such as the auditory domain, further studies are needed to test whether an impairment of sustained processing of task-irrelevant salient events in ADHD is evident across modalities. Third, as ADHD is a heterogeneous disorder and generalization to other samples with ADHD is therefore difficult, replication of these findings is warranted. Fourth, we could not relate our findings to underlying brain areas, which should be done in future studies.

Conclusion

The major aim of the present study was to investigate the mechanisms of attention allocation in adult ADHD by disentangling the specific effects of different kinds of salience, namely targetness, deviance and novelty. The findings do support deficient attention allocation in adults with ADHD, but suggest that the underlying mechanism is not a general deficit of top-down attentional processing of task-relevant events in ADHD or an increased distractibility by task-irrelevant novel events. The findings suggest decreased stimulus identification and are supportive of a disturbance in salience attribution to task-irrelevant novel events.

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CHAPTER 6

GENERAL DISCUSSION

In the present dissertation, I attempted to gain more insights into the processing of errors and other salient stimuli in ADHD. More specifically, I aimed to gain more knowledge on error awareness in ADHD and the processing of targets and novels. In this final chapter, I first give a recapitulation of the aims of this dissertation and an integrated overview of the empirical chapters, followed by a discussion of the theoretical, methodological and clinical implications. I will end with the formulation of some limitations of the conducted studies and some suggestions for future research.

RECAPITULATION OF RESEARCH GOALS

The goals of this dissertation were fourfold. To broaden the understanding of how we become aware of some errors while other errors remain unnoticed, some assumptions of the *accumulating evidence account* (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010) were first tested (*Chapter 2*). More specifically, by means of ERPs, two sources of error evidence were examined, namely visual sensory feedback and interoceptive awareness. These sources were hypothesized to underlie the emergence of error awareness and in turn mainly influence the late Pe, the presumed neural correlate of error awareness. A speeded Go/No-Go task with an explicit measure of error awareness was therefore implemented, which allowed us to distinguish between aware and unaware errors.

As the importance of interoceptive awareness for error awareness has been established (*Chapter 4*) and deficient error awareness has been suggested in ADHD (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013), a second exploratory aim of this dissertation was to investigate whether ADHD was characterized by an inability to become aware of bodily signals (*Chapter 3*). To this end, an objective heartbeat perception task and a subjective measure were administered.

The speeded Go/No-Go paradigm with an explicit measure of error awareness was used to gain more knowledge on deficient error awareness in ADHD by combining ERPs and a source localization technique to establish the underlying neural sources (*Chapter 4*). This third major goal of the dissertation was inspired by previous inconsistent research on error awareness in ADHD (Geburek et al., 2013; Shiels & Hawk, 2010) and the lack of an explicit measure of error awareness in previous studies (except for the study of O'Connell et al., 2009), which is needed to unequivocally establish deficient error awareness in this patient group.

Deficits in error processing in individuals with ADHD have been reported, but also deficits in the processing of other salient stimuli. The fourth goal of this dissertation was therefore to examine whether there is a deficit in processing of other salient stimuli in ADHD, which may suggest a general deficit in salience processing. By means of ERPs, the processing of salient targets, non-targets and novels was tested (*Chapter 5*) in a four-stimulus oddball task.

GENERAL OVERVIEW OF THE FINDINGS

Chapter 2. To investigate the assumption of the accumulating evidence account (Ullsperger et al., 2010) that visual sensory feedback and interoceptive awareness, two sources of error evidence arising at later stages in the post-error onset interval, underlie the emergence of error awareness and mainly influence the late Pe, a between-subjects study was conducted in typically developed adults in which visibility of the response hand was manipulated and interoceptive awareness was assessed by means of a heartbeat perception task. In line with previous research, the late Pe was larger for aware errors than for unaware errors or correct responses. With regard to the influence of sensory feedback on the late Pe, contrary to our predictions, a trend-significantly larger awareness effect (aware minus unaware errors) was found when visual sensory feedback from the response hand was not available compared to when it was. However, this could be explained by the observation that the ERN was modulated by error awareness, only when visual sensory feedback was available. In this condition, error awareness apparently started to arise earlier than when the response hand was not visible, as reflected in an enlarged late Pe amplitude and delayed error signaling in the latter condition. With regard to the influence of interoceptive awareness on the late Pe amplitude, individuals with higher interoceptive awareness also had larger Pe amplitudes to aware errors than individuals who were less proficient at the heartbeat perception task. Interestingly, this was only the case when visual sensory feedback from the response hand was available, which suggests that both sources of error evidence interact dynamically during the emergence of error awareness.

Chapter 3. To examine interoceptive awareness in ADHD, individuals with and without ADHD performed a heartbeat perception task, which is widely used to objectively assess interoceptive awareness. In addition, also a subjective measure (questionnaire) of interoceptive awareness was used. Adults with and without ADHD performed equally well on both the objective heartbeat perception task and subjective measure of interoceptive awareness.

Chapter 4. To unequivocally establish deficient error awareness in ADHD, a speeded Go/No-Go paradigm was implemented in which participants were instructed to signal error commission by pressing an extra response button. Unexpectedly, adults with

ADHD did not make more errors and were not less likely to signal these errors as consciously detected. The ERN, early Pe and late Pe were all modulated by error awareness. Surprisingly, not for the late Pe but for the early Pe, the awareness effect was marginally significantly smaller in individuals with ADHD than without ADHD. Source localization analyses revealed that this was accompanied with decreased activation in the left superior/middle frontal gyrus and increased activation of the right inferior frontal gyrus (rIFG). In the ADHD group, a negative correlation between the activation of the rIFG and the percentage of aware errors was found.

Chapter 5. By means of a four-stimulus oddball task in which task-relevant targets and task-irrelevant non-targets and novels were infrequently presented during a stream of frequent standards, the processing of other salient stimuli in ADHD was examined. Specific contrasts were applied to test for different types of salience, namely deviance, targetness and novelty and clear effects of these types of salience across several components were found. At the behavioral level, no group differences between adults with and without ADHD were observed. Irrespective of the type of salience, a marginally significant smaller P2 amplitude in the ADHD group was found. Contrary to our predictions, no evidence for a smaller P3b amplitude to targets and a larger novelty P3 to non-targets and novels in ADHD was found. However, only for adults with ADHD but not for adults without ADHD, a larger P3b to novels was apparent, indicating increased sustained processing of task-irrelevant novels.

INTEGRATION OF MAIN FINDINGS

Error processing

Supportive evidence for the accumulating evidence account. Conform the assumptions of the accumulating evidence account (Ullsperger et al., 2010), both visual sensory feedback and interoceptive awareness influenced the emergence of error awareness and in turn the late Pe. However, counter to our predictions, with regard to findings for visual sensory feedback, the awareness effect was larger when visual sensory feedback from the response hand was not available. In case of reduced availability of visual sensory feedback, error awareness seemed to emerge later in time.

As the influence of visual sensory feedback was also found for the ERN and was not specific for the late Pe, these findings do not fit the assumption of the accumulating evidence account (Ullsperger et al., 2010) that the ERN will mainly be influenced by sources that are quickly available after error commission, such as the mismatch between the actual and the intended response (Coles, Scheffers, & Holroyd, 2001) or post-response conflict (Carter et al., 1998). However, these findings do confirm that error awareness is the result of an accumulation of error evidence and that error awareness arises later in time when an important source of error evidence is not available. As the current study is the first to show the importance of visual sensory feedback for the emergence of error awareness, findings have to be replicated.

With regard to findings for interoceptive awareness, our findings are in accord with studies showing that only aware errors are accompanied by changes in autonomic activity, such as heart rate deceleration (Danev & Dewinter, 1971; Hajcak, McDonald, & Simons, 2003; Wessel, Danielmeier, & Ullsperger, 2011), increase in pupil size (Critchley, Tang, Glaser, Butterworth, & Dolan, 2005) and larger skin conductance responses (Hajcak et al., 2003) as well as the fact that enhanced activation of the (anterior) insula has been linked to both error awareness and interoceptive awareness (Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004; Hester, Foxe, Molholm, Shpaner, & Garavan, 2005; Klein et al., 2007). This is furthermore in line with the study of Sueyoshi and colleagues (2014) that had previously found a significant positive correlation between the mean heartbeat perception score and the amplitude of the late Pe. However, this study did not make use of an explicit measure of error awareness, which is needed to unequivocally establish a link between interoceptive awareness and error awareness and in extension the late Pe. In addition, in this study, the correlation with interoceptive awareness was found specifically for the late Pe as it was absent for the ERN, which fits nicely with the assumption of the accumulating evidence account (Ullsperger et al., 2010) that sources of error evidence that become available at later stages in the post-error onset interval mainly influence late correlates of error processing, namely the late Pe. In conclusion, evidence strongly supports the assumptions of the accumulating evidence account in that several sources of error evidence become available at different stages after error commission and timely influence the emergence of error awareness. More specifically, becoming aware of errors was shown to be dependent upon visual

sensory feedback from the response hand and the ability to become aware of bodily signals. Further research should look into other sources of error evidence, such as auditory sensory feedback (i.e., the sound elicited by the response button), that possibly contribute to the emergence of error awareness.

Although no predictions regarding the mutual influence of visual sensory feedback and interoceptive awareness during the emergence of error awareness are made by the accumulating evidence account (Ullsperger et al., 2010), our findings suggest an interaction effect between both sources of error evidence. Interoceptive awareness only supported the emergence of error awareness when visual sensory feedback from the response hand was available which suggests that both sources of error evidence are interdependent. Interaction effects between exteroceptive and interoceptive signals, which are possibly integrated online by the anterior insula (Simmons et al., 2013), have previously been observed in studies on self-experience and body ownership (Ainley, Maister, Brokfeld, Farmer, & Tsakiris, 2013; Ainley, Tajadura-Jiménez, Fotopoulou, & Tsakiris, 2012; Suzuki, Garfinkel, Critchley, & Seth, 2013). For example, attention to the self as perceived exteroceptively (e.g., through vision of one's own face) improves performance on the heartbeat perception task. More research is needed to elucidate this interaction effect during the emergence of error awareness as well as explore possible interactions with other exteroceptive sources of error evidence.

Preserved interoceptive awareness in ADHD. As the importance of interoceptive awareness for the processing of errors was established and research suggested deficient error awareness in ADHD (Geburek et al., 2013; O'Connell et al., 2009), the ability to become aware of bodily signals was explored in ADHD. This hypothesis was furthermore inspired by theoretical models as well as empirical findings underscoring the importance of interoceptive awareness for self-regulation and adaptive behavior. Interoceptive awareness has not only been implicated in error awareness (Sueyoshi et al., 2014; Ullsperger et al., 2010) but also in many other cognitive functions important for self-regulation that have previously been shown to be disrupted in ADHD, such as emotion processing and regulation (Herbert, Pollatos, & Schandry, 2007; Herrmann et al., 2009; Pollatos, Herbert, Matthias, & Schandry, 2007; Shaw, Stringaris, Nigg, & Leibenluft, 2014) and post-error slowing (Balogh & Czobor, 2014; Sueyoshi et al., 2014). In addition, according to the *cognitive energetic model* (Sanders, 1983) and the *state regulation*

account (Sergeant, 2005; Sergeant, 2000; van der Meere, 2005), monitoring the current energetic state is pivotal for effective state regulation. As the models include feedback loops from the energetic (arousal/activation) pools to the evaluation mechanism, information on the momentary bodily state thus seems to be important for effective state regulation. State regulation deficits observed in ADHD may therefore be associated with an inability to become aware of the bodily signals that provide information on the current energetic state. The findings suggest however a preserved monitoring of bodily state in adult ADHD, which tentatively suggests that deficient error awareness and more broadly, the state regulation deficit and related self-regulatory difficulties in ADHD may not be due to an inability to become aware of bodily signals. As this is the first study to show that the basic skill of interoceptive awareness is intact in ADHD, replication of the findings is needed. In addition, future research should explore whether becoming aware of bodily signals is impaired during daily life or whether interoceptive information is wrongly applied or interpreted in ADHD. More generally, it could be that the integration of interoceptive with exteroceptive information is disrupted in ADHD.

Deficient error awareness in ADHD. Counter to our predictions and not in line with the study of O'Connell et al. (2009), individuals with and without ADHD made an equal amount of aware errors. Unlike the findings of the meta-analysis on error processing in adults with ADHD (Geburek et al., 2013), but in line with the study of O'Connell et al. (2009) that made use of an explicit measure of error awareness, the ERN to aware errors was not attenuated in ADHD. Contrary to our predictions and the findings of O'Connell et al. (2009), the late Pe to aware errors was not smaller in adults with ADHD compared to adults without ADHD, which is in line with the finding of preserved interoceptive awareness in adults with ADHD (*Chapter 3*). Instead, we found a smaller error awareness effect for the early Pe in adults with ADHD. A smaller early Pe in adults with ADHD has been reported before but independent of awareness by O'Connell et al. (2009), who found this component to be smaller for aware errors, unaware errors and correct responses in adults with ADHD. Interestingly, also in children with ADHD, a smaller early Pe amplitude has been reported before, although the paradigm in that study did not make use of an explicit measure of error awareness (Van De Voorde, Roeyers, & Wiersema, 2010). In general, our ERP findings suggest deficient error awareness in ADHD, more specifically at the level of the early Pe. However, it is still unknown how the

pattern of ERP results (i.e., a normal ERN, a smaller early Pe and a normal late Pe in ADHD) can be explained, even more so when considering that the emergence of error awareness is assumed to be an accumulation of error evidence with repercussions at each of these neural correlates of error processing. Interestingly, the late Pe has previously been linked to subjective confidence (Boldt & Yeung, 2015). It could therefore be that the accumulation of error evidence is more noisy (i.e., impaired early Pe) in ADHD, but that they feel as confident about having made an error as typically developed adults. Indeed, individuals with ADHD tend to overestimate their performance on a variety of tasks (Knouse, Bagwell, Barkley, & Murphy, 2005). However, more research is clearly needed to investigate this hypothesis.

The smaller awareness effect at the early Pe level in ADHD was accompanied by less activation in the left superior middle frontal gyrus and more activation of the rIFG. Specifically for the ADHD group, the amplitude of the latter region was also negatively correlated with the percentage of aware errors. With regard to the middle frontal gyrus, increased activation of this region for aware to unaware errors has previously been reported (Hester et al., 2005). This region is also part of the default-mode network, a network supporting internally oriented cognition (Sidlauskaite et al., 2014), and contributions of this network to error awareness have been previously reported (Allen et al., 2013), which is in line with the idea that signaling an error as consciously detected relies (partly) on introspective abilities. Therefore, the decreased activation of this region in the ADHD group may suggest that this patient group was less internally focused during the meta-cognitive process of error awareness. With regard to the rIFG, this region is part of the central executive network, which is a network activated during task performance. The rIFG has been related to response inhibition and this area is consistently found impaired in ADHD. Increased as well as decreased activation in ADHD has been observed for this region during response inhibition (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Lei et al., 2015; Rubia, 2011). This finding suggests that a region responsible for response inhibition is still activated in the ADHD group 200 ms after error commission. However, further research is needed to establish how the increased activation of this area is related to diminished error awareness. On the one hand, it could be that the sustained activation of this area leads to less error awareness.

On the other hand, it could also be that less error awareness leads to continued inhibition.

Implications for the neural correlates of error processing and awareness. The ERN was modulated by error awareness in the studies presented in *Chapter 2* (although at more posterior sites and specifically in case of availability of visual sensory feedback from the response hand) and in *Chapter 4*, which is in contrast to studies finding no differences in the ERN amplitude for aware and unaware errors, but is in line with studies reporting larger ERN amplitudes for aware than unaware errors (see for overview Wessel, 2012). This finding is furthermore in accord with the recently advocated notion that the ERN is sensitive to error awareness under specific circumstances (Shalgi & Deouell, 2012, 2013; Wessel, 2012). It has previously been shown that the modulation of the ERN by error awareness is dependent upon the method used to report errors, namely signaling a consciously detected error, the use of forced choice ratings (Wessel, 2012) or post-decision wagering (Shalgi & Deouell, 2012). This study is the first to show that the sensitivity of the ERN to error awareness is also dependent upon (the task demands of) the paradigm, however, replication of the findings is needed.

In addition, in both studies, also an early Pe was elicited (although not described in *Chapter 2*) which was shown to be sensitive to error awareness as it was evoked only for aware errors and absent for unaware errors and correct responses. Although the functional significance of the early Pe is not yet clear and although some authors have hypothesized that this deflection is functionally similar to the ERN (Debener et al., 2005; Luu, Tucker, & Makeig, 2004; Van Veen & Carter, 2002), both deflections have different topographies (Arbel & Donchin, 2009; Endrass, Klawohn, Preuss, & Kathmann, 2012), different neural generators and are differently affected in ADHD (*Chapter 4*). This clearly indicates that the ERN and early Pe reflect distinct stages of error processing. However, further research on the functional significance of the early Pe is warranted.

In the studies presented in *Chapter 2* and *4*, all correlates of error processing (i.e., ERN, early Pe, late Pe) were thus modulated by error awareness. These findings therefore call into question the prevailing view of the late Pe as the supposed neural correlate of error awareness and the dichotomy in literature between unconscious and conscious processing as reflected by the ERN and late Pe. However, in light of the

accumulating evidence account (Ullsperger et al., 2010), dependent on whether and when sources of error evidence become available after error commission, all correlates of error processing can be influenced by these sources during the emergence of error awareness. In light of this, the late Pe can be seen as the final stage of this accumulation of evidence. How conscious processing is reflected in the correlates of error processing therefore seems to depend on several methodological factors, such as the experimental paradigm used. Future research is therefore warranted to implement a paradigm that is optimally adjusted to investigate error awareness. This optimal error awareness paradigm will be discussed in more detail in the section on future research.

Processing of other salient stimuli

The processing of salient targets, non-targets and novels. By controlling for confounding factors related to the conceptualization of novels and by applying specific contrasts to test for pure effects of different types of salience, specific effects for targetness, deviance and novelty across the components of interest were observed. The findings therefore corroborate the notion that stimuli can be salient for different reasons and support the definition of salience put forward in this dissertation, which incorporates both bottom-up aspects of the stimulus as well as top-down processes (Cunningham & Brosch, 2012; Uddin, 2014). By means of this approach, counter to the prevalent view, it was additionally shown that both the processing of targets and novels occur at early and late stages of stimulus processing, respectively. Effects of target processing were already apparent at the level of the P2 component, while sustained processing of novels was reflected in a positive-going slow wave. The findings also have implications for the functional significance of several components of stimulus processing. It was shown that the novelty P3 reflects deviance rather than novelty, in accord with previous observations (Schomaker & Meeter, 2015). In contrast to the novelty P3, the N2 was sensitive to novelty (Schomaker & Meeter, 2015), as an added effect of novelty over deviance was observed. However, the N2 as well as the P2 were sensitive to all types of salience, which suggests that these components can be thought of as general markers of salience.

The processing of salient targets and novels in ADHD. Support for normal processing of non-targets in ADHD was provided, which furthermore confirms the notion that studies should make a clear distinction between deviant non-targets and pure novels. Contrary to ample previous observations (Johnstone, Barry, & Clarke, 2013; Marzinzik et al., 2012; Szuromi, Czobor, Komlósi, & Bitter, 2011), no evidence was provided for impaired target processing in ADHD at the behavioral or neural level. Some studies have reported normal P3b amplitudes in ADHD, but under specific circumstances, namely in case of a high event rate (i.e., the presentation rate of the stimuli) as opposed to a slow event rate (Wiersema, van der Meere, Antrop, & Roeyers, 2006; Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006). These studies as well as the findings from this dissertation therefore suggest that task performance and in extension a deficit in top-down allocation of attentional resources in ADHD may be state-specific or context-dependent. This is in line with the current view on ADHD as a context dependent disorder of self-regulation, which is supported by neuropsychological theories such as the state regulation deficit account (Sergeant, 2000; Sonuga-Barke, Wiersema, van der Meere, & Roeyers, 2010; van der Meere, 2005). This account postulates that ADHD is characterized by a difficulty in allocating the additional effort needed to adjust the energetic (arousal/activation) state required for optimal task performance. Interestingly, performance improvements in ADHD have been observed after the presentation of novels (Tegelbeckers et al., 2016; van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007). Although speculatively at this stage, it could be hypothesized that the presentation of novels (perhaps in combination with the presentation rate of the stimuli) in the four-stimulus oddball task was stimulating enough to keep the energetic state of the individuals with ADHD at an optimal level, which was reflected in good task performance. Further research should investigate the conditions in which the presentation of novels is beneficial for task performance in ADHD as well as try to uncover the underlying mechanism through which these novels have a beneficial effect on task performance in ADHD. This could perhaps be by elevating the arousal level, in line with studies showing performance improvement in ADHD by presenting white noise as external stimulation (Söderlund, Sikström, Loftesnes, & Sonuga-Barke, 2010; Söderlund, Sikström, & Smart, 2007).

Evidence for deficient attention allocation in ADHD was provided, however, the findings suggest that this is not due to an increased distractibility by task-irrelevant novels as evidenced by a normal novelty P3 (and N2) to novels but by a disturbance in salience attribution to task-irrelevant novels as reflected by a larger P3b to novels in ADHD. The finding of a normal novelty P3 amplitude to novels in ADHD adds to the inconsistencies in the literature regarding this component (Gumenyuk et al., 2005; Jonkman et al., 2000; Marzinzik et al., 2012; van Mourik et al., 2007). A P3b to novels was apparent only in the ADHD group, which suggests enhanced sustained processing of salient task-irrelevant information in this group. Disrupted novelty processing at the P3b level in ADHD has already been reported before (Marzinzik et al., 2012). It is in agreement with a dysfunction of stimulus weighing in ADHD, since this group clearly processed task-irrelevant distracting further as task-relevant stimuli. Future research on the abnormal salience attribution of novel information in ADHD is warranted.

No support for a general salience processing deficit in ADHD. When combining the findings from *Chapters 3*, *4* and *5*, indirect support against the hypothesis of a general salience processing deficit in ADHD has been provided. Preserved processing of targets and non-targets was observed in ADHD, while processing of aware errors and novels was impaired. In addition, the fact that the processing of (aware) errors and novels was impaired in ADHD while the processing of targets was not impaired and the fact that impaired processing of these stimuli in ADHD was evidenced at different levels during processing indirectly speaks against the idea of a resemblance in the processing of errors and targets on the one hand and errors and novels on the other hand. Indeed, two hypotheses have previously been put forward in literature, namely that the late Pe to aware errors resembles a P3b to motivational significant errors (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005; Ridderinkhof, Ramautar, & Wijnen, 2009) and that the processing of errors resembles the processing of novels (Wessel, Danielmeier, Morton, & Ullsperger, 2012). Both lines of research would benefit from studies that compare these different salient stimuli within the same paradigm. This paradigm should also incorporate an explicit measure of error awareness and try to identify the underlying neural sources that are sensitive to the processing of all these kinds of salient stimuli.

In this dissertation, since data on the processing of errors, targets and novels is available across paradigms, a first attempt to provide an answer on the resemblance in processing of errors and targets on the one hand and errors and novels on the other hand was undertaken by specifically testing the two suggested hypotheses. To capture more global differences/similarities between the processing of these different salient stimuli, instead of standard ERP analyses, an exploratory topographical mapping analysis of the ERP data was performed. This analysis was carried out with CARTOOL software (Version 3.34; developed by D. Brunet, Functional Brain Mapping Laboratory, Geneva, Switzerland) and performed on group-averaged data from -200 ms before until 1000 ms after the response in case of an error or the stimulus in case of a target or novel. The group consisted of 79 participants of which reliable data (i.e., enough aware and unaware errors or novels) was available across paradigms, namely for both the speeded Go/No-Go task and the four-stimulus oddball task. Note that some participants included in this exploratory analysis were from studies not included in this dissertation. Moreover, several confounds should be taken into account. This participant sample consisted of individuals with and without ADHD (23 vs. 56 participants), aware and unaware errors trials were computed either across the easy and difficult No-Go conditions or only for the difficult condition of the speeded Go/No-Go task, and two versions of the four-stimulus oddball tasks were included (novels with meaning vs. novels without meaning).

In a first step, a spatiotemporal segmentation algorithm (Pascual-Marqui, Michel, & Lehmann, 1995) characterizes the most dominant scalp topographies appearing in the group-averaged ERPs of each condition and over time. This segmentation procedure provides correlations between scalp topographies that give an indication on the similarity between these scalp topographies. For the analysis on the resemblance between the late Pe to aware errors and the P3b to targets, a solution with 15 maps explained 95% of the variance (see Figure 1A). The scalp map corresponding to the Pe (map#6) was chosen, while map (map#3) was chosen as the scalp map representing the P3b to targets. The correlation between those maps was r = .65 which suggests that they were quite identical. For the analysis on the resemblance between the processing of errors and novels, a solution with 14 maps explained 95% of the variance (see Figure 1B). The scalp map corresponding to the Pe (map#7) was chosen, while map (map#12)

was chosen as the scalp map representing the novelty P3 to novels. The correlation between those maps was r = .36 which suggests that they share some similarities.

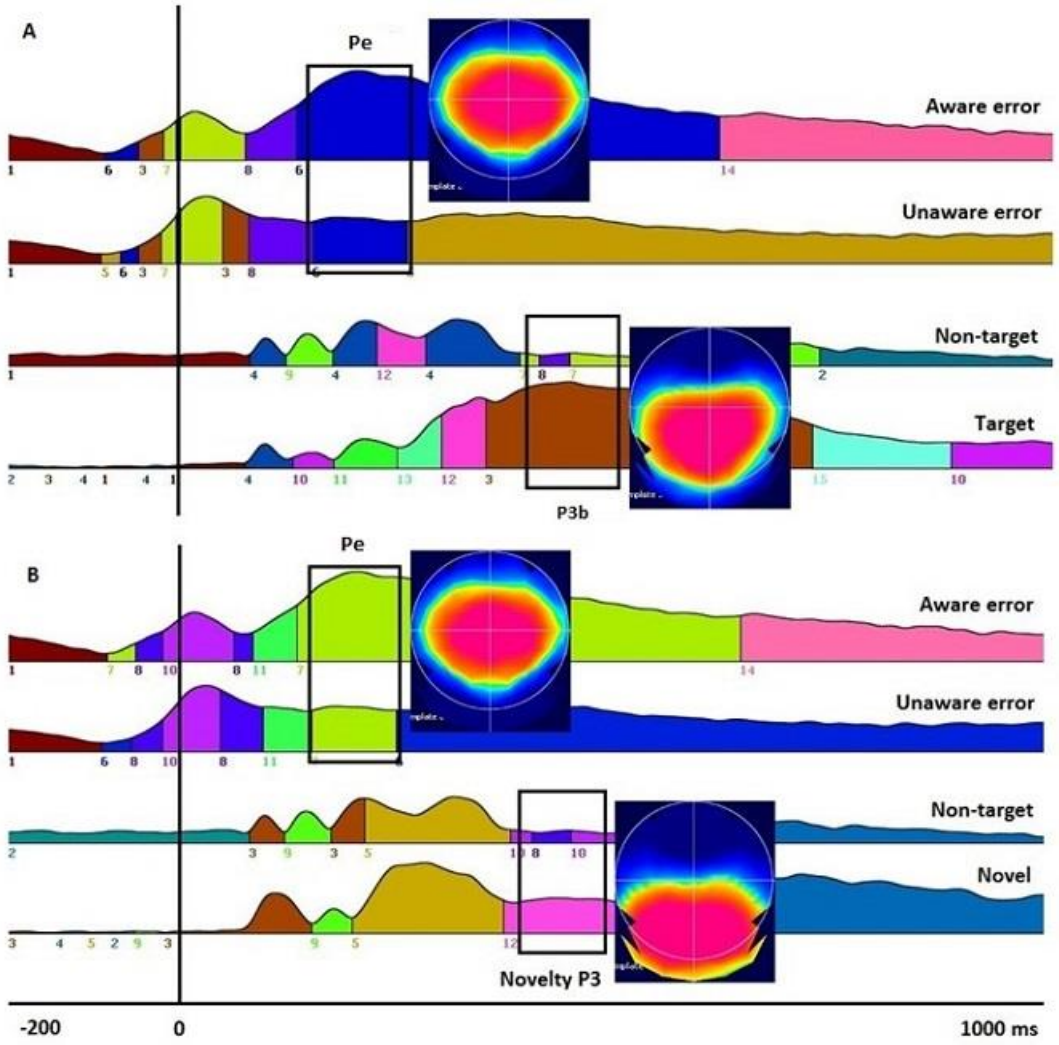

Figure 1. (A) Topographic maps corresponding to the Pe for aware errors (map#6) and the P3b for targets (map#3). (B) Topographic maps corresponding to the Pe for aware errors (map#7) and the novelty P3 for novels (map#12). The indicated time windows refer to the windows used for fitting the dominant scalp topographies, spanning from 150 to 250 ms after response onset for aware and unaware errors and from 400 to 500 ms after stimulus presentation for non-targets, targets and novels.

In a second step, these dominant scalp topographies are then fitted to the individual ERP data to quantitatively determine their representation across subjects and conditions. For both analyses, the two selected maps were fitted back to the individual ERP data of the four conditions (aware errors, unaware errors, targets/novels, non-targets) for the time window in which these maps were most pronounced, namely 150 and 250 ms after the response for the aware and unaware errors and between 400 and 500 ms after stimulus presentation for targets/novels and non-targets. By means of this fitting procedure, Global Explained Variance (GEV or goodness of fit) values of these maps per condition were obtained that were used for subsequent statistical testing. As expected, the GEV of the Pe map was larger for the aware than unaware condition. The GEV of the P3b map was larger for the target than non-target condition, while the GEV of the novelty P3 map was larger for the novel condition than the non-target condition.

If there is a large overlap in the resemblance between the topography of the Pe and the P3b/novelty P3, I expected that both maps would explain a large proportion of variance for both relevant conditions, namely the aware error and target/novel conditions, such that the pattern of data suggested that one particular map did not dominate over the other but were hard to discriminate from each other by the CARTOOL software. I expected that these topographies would explain few variance for the unaware error and non-target condition. The GEV values were entered in a repeated measures ANOVA with within-subjects factors task (2 levels: speeded Go/No-Go task vs. four-stimulus oddball task), condition (2 levels: aware error vs. unaware error or target/novel vs. non-target) and map configuration (2 levels: Pe map vs. P3b map/novelty P3) and I expected a significant three-way interaction between task, condition and map configuration. For the analysis on the resemblance between the late Pe to aware errors and the P3b to targets, a significant three-way interaction between task, condition and map configuration was observed ($F(1, 78) = 22.42$, $p < .001$, $\eta^2_p = .22$) (see Figure 2A). For the analysis on the resemblance between the late Pe to aware errors and the novelty P3 to novels, a significant three-way interaction between task, condition and map configuration was also revealed ($F(1, 78) = 25.70$, $p < .001$, $\eta^2_p = .25$) (see Figure 2B). However, for both analyses, the pattern of data was not as hypothesized, namely both maps did not explain a large proportion of variance for both the aware error and target/novel condition and few variance for the unaware error and non-target condition.

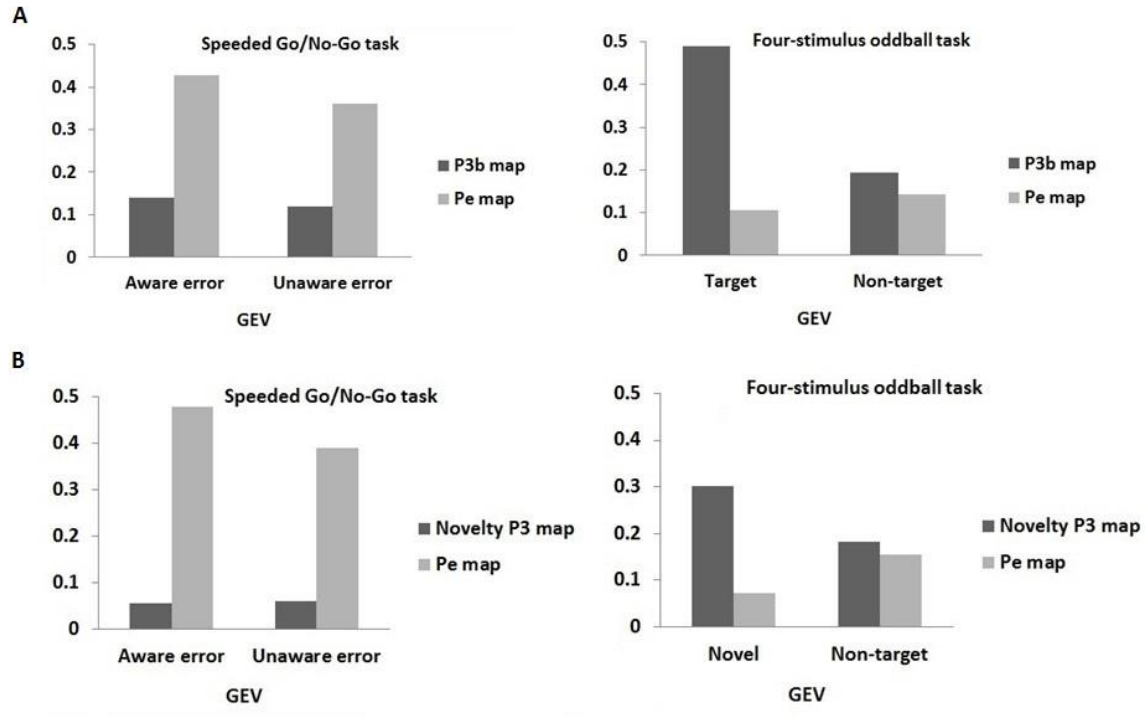

Figure 2. (A) GEV values of the Pe map and P3b map for each condition, separately for each task. (B) GEV values of the Pe map and novelty P3 map for each condition, separately for each task.

Several important remarks have to be made. The identified dominant scalp topography for the Pe had a central distribution and therefore corresponds better with the early Pe than the more centro-parietal late Pe. However, the hypotheses regarding a resemblance between the processing of errors and the processing of targets refers to the late Pe. The topography of this central Pe map also shared a lot of similarities with the topography of the map that represented the unaware error. Moreover, the map corresponding to the novelty P3 also resembled more a P3b. Therefore, no firm conclusions on the resemblance of the processing of errors and targets on the one hand and errors and novels on the other hand can be drawn from these analyses.

Additional deficits in ADHD. Irrespective of the type of salience, a smaller P2 amplitude was observed in ADHD, suggestive of disturbed early automatic attentional processing in ADHD. Abnormal P2 amplitudes in ADHD have previously been found. However, research on the P2 component in adult ADHD is scarce with only one study reporting larger P2 amplitudes to targets (Barry et al., 2009). In studies with children with ADHD, both larger and smaller P2 amplitudes have been reported (Johnstone et al., 2013; Wiersema, van der Meere, Van Coster et al., 2006), but smaller P2 amplitudes were explained in terms of a stimulus identification deficit (Brown et al., 2005) and/or are believed to be reflective of an inhibitory process missing in the transition from exogenous to endogenous processing (Oades, Dittmann-Balcar, Schepker, Eggers, & Zerbin, 1996). To our knowledge, this is the first study to observe generally smaller P2 amplitudes in adult ADHD, which impedes drawing firm conclusions on the meaning of these findings. In the study reported in *Chapter 5*, the P2 was found to be a general marker of salience, as it was sensitive to all types of salience. This finding may therefore suggest a deficit in the identification or processing of salient stimuli in general. More research is clearly needed to delineate the functional significance of this component in attention allocation and its role in ADHD.

IMPLICATIONS

Theoretical and methodological implications

The findings have important implications for the functional significance of the neural correlates of error processing. It was shown that all correlates can be modulated by error awareness, but under specific circumstances. In particular, the view of the late Pe as the supposed neural correlate of error awareness is questioned. From a methodological perspective, although the use of an error-signaling has been criticized (see below), the findings in this dissertation show the importance of incorporating an explicit measure of error awareness into the paradigm used to investigate error awareness. Furthermore, the findings have important implications for the functional significance of the neural correlates of stimulus processing. It was shown that the processing of targets and novels occur at early and late stages of stimulus processing. Moreover, it was shown that the novelty P3 reflects deviance and that, in contrast to the

novelty P3, the N2 is sensitive to novelty (Schomaker & Meeter, 2015), and that the N2 and P2 components seem to be sensitive to salience in general.

The finding that interoceptive awareness supports the emergence of error awareness is in accord with the idea that interoceptive awareness has a pivotal role in the processing of salient external stimuli, as postulated by the accumulating evidence account (Ullsperger et al., 2010). This idea that the ability to consciously perceive bodily signals influences many mental processes has already been endorsed for a long time in theories of emotion processing, such as the *somatic marker hypothesis* (Damasio, 1996). This hypothesis postulates that bodily changes (i.e., somatic markers) induced by an external event are fed back to the brain to signal the significance of this event and this way influence the mental processes associated with this event. Research on emotion processing provided the first support for the important role of interoceptive awareness in the emotional experience (Herbert et al., 2007; Pollatos et al., 2007). More recently, interoceptive awareness has been shown to influence decision-making (Werner et al., 2013), post-error adaptation (Sueyoshi et al., 2014) and memory (Garfinkel et al., 2013). This study expands these findings to the study of error awareness and therefore also yields support for the theories of emotion processing, more specifically the somatic marker hypothesis (Damasio, 1996).

Support for deficient error awareness in ADHD has been provided. In addition, the basic skill of interoceptive awareness was preserved in ADHD. This suggests that the deficient error awareness in ADHD is probably not due to an inability to become aware of the bodily signals. Thus, the question remains how this diminished error awareness can be explained. First, on the one hand, it could be related to processes that already take place before actual error commission. There is ample evidence that errors are already foreshadowed by maladaptive changes in brain activity and that momentary lapses of attention are related to subsequent error commission (Cavanagh, Cohen, & Allen, 2009; Eichele, Juvodden, Ullsperger, & Eichele, 2010; Mazaheri, Nieuwenhuis, Van Dijk, & Jensen, 2009; Ridderinkhof, Nieuwenhuis, & Bashore, 2003). These spontaneous attentional fluctuations are thought to be the result of decreased deactivation of the default-mode network. This is in agreement with the *default-mode interference hypothesis* (Sonuga-Barke & Castellanos, 2007) that postulates that in ADHD the default-mode network is not adequately suppressed by the salience network which eventually

leads to performance errors. Evidence for aberrant functional connectivity in this network in ADHD has been provided (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2015). Interestingly, only one fMRI study has examined whether aberrant default-mode network activity and thus momentary lapses of attention precede errors in children with ADHD, but has failed to provide evidence (Spinelli et al., 2011). However, no study to date has examined this intriguing question in a paradigm that incorporated an explicit measure of error awareness. It could be that error-preceding brain activity is altered in ADHD and that this explains diminished error awareness in this patient group. It could be that aware and unaware errors are preceded by different patterns of maladaptive brain activity and that this may relate to diminished error awareness in ADHD. To provide direct support for this hypothesis, it is pivotal to perform a single-trial analysis. By means of this type of analysis, error precursors can be directly linked to the variability in the Pe amplitude and provide valuable knowledge on deficient error awareness.

Second, on the other hand, the diminished error awareness in ADHD may be related to the increased activation of the rIFG in this patient group, which seems to suggest sustained inhibition of the inaccurate Go response. Increased activation of the rIFG in the ADHD group was observed around 200 ms after error commission. On the one hand, it could be that the sustained inhibition in the ADHD group leads to diminished error awareness. On the other hand, it could be that deficient error awareness in ADHD leads to the continued inhibition. More research is needed to establish the (causal) direction of this effect. To this end, neuroimaging methods can be used to study the activation of the rIFG prior to error commission. This would furthermore provide information on whether deficient error awareness in ADHD can be explained in terms of a deficit in response inhibition, which would be in line with the *executive dysfunction theory* (Barkley, 1997).

The finding of preserved interoceptive awareness in ADHD has implications for the state regulation deficit model (van der Meere, 2005) as it suggests that self-regulatory difficulties in ADHD may not be related to the ability to become aware of bodily signals and thus the monitoring of the bodily state. Therefore, the question of what exactly gives rise to the self-regulatory problems characterizing this patient group still needs to be answered. It could still be that individuals with ADHD have difficulties in allocating the additional effort to compensate for suboptimal conditions, despite the correct

evaluation of bodily state. However, the fluctuating performance in individuals with ADHD also questions whether the self-regulatory deficits in ADHD indeed reflect a difficulty in allocating the required effort or rather an unwillingness to perform well in specific circumstances. The self-regulatory difficulties in ADHD may therefore rather be related to a generally altered motivational attitude. Motivation and effort allocation are strongly related concepts (Sanders, 1983) and motivational and reward processing deficits in ADHD have been postulated. For example, it has been shown that ADHD is associated with an altered reinforcement sensitivity (Luman, Tripp, & Scheres, 2010). The prominent *delay aversion theory* relates the context-dependent deficits in ADHD to an altered motivational style and assumes that these deficits are related to an aversion to delay in ADHD (Sonuga-Barke, Taylor, Sembi, & Smith, 1992). Finally, the self-regulatory difficulties in ADHD could also be related to a problem in the processing of performance feedback. Some studies suggest that individuals with ADHD process feedback to a lesser extent, which may be related to difficulties in adaptive control (Groen et al., 2008; Groen, Mulder, Wijers, Minderaa, & Althaus, 2009). For example, electrophysiological studies in ADHD have shown alterations in the feedback-related negativity, which is the feedback-variant of the ERN (Groen, Tucha, Wijers, & Althaus, 2013; Van Meel, Heslenfeld, Oosterlaan, Luman, & Sergeant, 2011; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005).

Clinical implications

All studies included in this dissertation were experimental in nature, which often makes translation to the clinical practice more difficult. Therefore, the clinical implications are formulated rather tentatively.

The finding of deficient error awareness in ADHD, together with previously provided evidence in children as well as adults with ADHD (Geburek et al., 2013; O'Connell et al., 2009; Shiels & Hawk, 2010), suggests that this error awareness deficit is an important aspect of the ADHD syndrome, already present in childhood and persisting into adulthood. Becoming aware of errors is pivotal for flexible behavioral adjustments and for learning not to repeat inadequate behavior in the long term. Deficient error awareness may therefore be best targeted by (early) intervention programs. Treatment may include psychological interventions or stimulant medication, or ideally a

combination of both. However, to date, little is known about the impact of these treatment programs on deficient error awareness (Sonuga-Barke et al., 2013). Importantly, a few studies suggest normalization of the Pe amplitude after use of methylphenidate (Groen et al., 2008; Jonkman, van Melis, Kemner, & Markus, 2007), which implies that the use of stimulant medication can counteract deficient error awareness. Future research examining the usefulness of treatment programs for deficient error awareness in ADHD is warranted.

The findings suggest increased sustained processing of task-irrelevant novels in ADHD. In daily life, it is important to make a rapid distinction between novel stimuli that either do not need further processing or require an adequate behavioral response. The findings suggest that individuals with ADHD are impaired in making this distinction as task-irrelevant novels were processed further in this group. Moreover, on the one hand, it has been shown that distracting novel stimuli can have a detrimental effect on task performance in ADHD (Gumenyuk et al., 2005). On the other hand, in some circumstances, the presentation of distracting novels can have beneficial effects on performance in ADHD (Tegelbeckers et al., 2016; van Mourik et al., 2007). If individuals with ADHD are impaired in making a distinction between novels that require further processing and novels that do not, and they show sustained processing of task-irrelevant novels, the question remains when the presence of novels will have a detrimental or beneficial effect on task performance. Identifying these conditions is important as this has implications for treatment optimization. For example, the classroom or work settings can be adjusted to the individual with ADHD so that optimal conditions are created for task performance.

Related to this, the data insinuates that the processing of task-relevant stimuli is not always disrupted in ADHD as a normal P3b amplitude to targets was observed in this patient group. This implies that the context or state of the individual with ADHD is important for task performance in this patient group. This normal processing of task-relevant stimuli in the ADHD group may be the result of the stimulating nature of the four-stimulus oddball task. It has been shown before that external stimulation, such as a high event rate of stimuli, the presentation of white noise and the presentation of novels can have beneficial effects on the performance in ADHD (Börger & van der Meere, 2000; Tegelbeckers et al., 2016; van Mourik et al., 2007; Wiersema, van der

Meere, Antrop et al., 2006; Wiersema, van der Meere, Van Coster et al., 2006). Whether the state-dependent processing of task-relevant stimuli in ADHD can be influenced by external stimulation with the purpose of optimizing task performance has to be established by further research, since identifying the conditions in which performance is improved by external stimulation is pivotal for clinical interventions.

LIMITATIONS

Several specific limitations were already described in each of the empirical chapters. In this section, some limitations spanning several empirical chapters of the dissertation will be outlined.

First, some concerns regarding the characteristics of our samples have to be formulated. In general, although comparable to previous studies, the sample sizes were relatively small. Possible existing behavioral or ERP differences between groups might have not been detected due to insufficient power. In addition, individuals of the control and ADHD group were relatively well-functioning as the mean IQ scores were in the upper average and average range, respectively. Finally, the considerable overlap among the participants samples across the studies of *Chapter 3*, *4* and *5* may limit the generalizability of the findings.

Second, some specific concerns regarding the characteristics of our sample of adults with ADHD are outlined. The ADHD group was a community sample, which is characterized by less symptom severity and impairment, as opposed to clinical samples (Brassett-Harknett & Butler, 2007). In addition, in line with the prominent clinical heterogeneity of ADHD, our ADHD sample comprised different subtypes of ADHD (i.e., predominantly inattentive subtype and combined subtype but not predominantly hyperactive/impulsive subtype) and was characterized by a variety of comorbid disorders. Additional exploratory analyses controlling for symptom severity, comorbidity, subgroups and even gender revealed no major changes in our findings. In addition, history and duration of stimulant or other psychoactive medication use was not taken into account. It can therefore not be fully excluded that medication use may have influenced our findings. However, an additional exploratory data check in *Chapter*

3 did not reveal differences between individuals with ADHD who were or were not taking medication. Furthermore, individuals with ADHD were asked to interrupt their medication 48 hr prior to participation in the experiments. Finally, only self-report measures were used in the studies and were not complemented by informant reports completed by significant others. Although adults with ADHD appear to be the best informants with regard to their symptoms, they tend to underreport the severity of their symptoms. Informant report may be used to get additional information on symptoms and impairment (Kooij et al., 2008). Moreover, all individuals with ADHD had received a formal diagnosis by a specialist team and this diagnosis was verified with a diagnostic interview.

Third, as ADHD is a heterogeneous disorder and its etiology multifactorial, the sample in the studies from this dissertation is therefore not completely representative of the disorder. The observed group differences can therefore not be generalized to all individuals with ADHD. Moreover, although differences were observed between individuals with and without ADHD at the group level and conclusions are based on a group-level analysis, inferences cannot be made about all individuals that belong to that group.

Fourth, there was an imbalance between conditions in the amount of trials used for ERP averaging in the speeded Go/No-Go task and the four-stimulus oddball task. This imbalance produces a mismatch of power between conditions, which can be reflected in the reliability of the ERP waveforms computed as ERPs are sensitive to the signal-to-noise ratio. In the speeded Go/No-Go task, participants had to respond to a Go stimulus on 60% of trials (216 Go trials), while they had to inhibit a response on 40% of trials (144 No-Go trials). In addition, participants had to signal a consciously detected error and aware errors were less frequent than unaware errors. A sufficient amount of correct responses (hits) and unaware errors were made for reliable ERP analyses. Specifically for the amount of aware errors, studies have shown that the signal-to-noise ratio of the Pe does not change anymore after 4 trials when more trials are added and that the Pe can be reliably quantified using a minimum of 6 error trials (Olvet & Hajcak, 2009). The number of aware error trials included in our studies was therefore sufficient for reliable ERP analyses. In the four-stimulus oddball task, in 70% of trials a standard (280 trials) was presented as opposed to a target, non-target and novels in 10% of the trials (40

trials each). In addition, for each individual separately, novels were excluded when they were associated with meaning as assessed by a rating, causing an even greater imbalance in the amount of trials. However, a sufficient amount of standard, target and non-target trials were presented for reliable ERP analyses. Although the power issue relates more to the novel trials, the lowest amount averaged for ERP analyses consisted of 12 novel trials, which is also sufficient for reliable ERP analyses.

Fifth, some other methodological considerations regarding the speeded Go/No-Go task have to be mentioned. Some participants were excluded because of a lack of aware errors, probably due to the use of an error signaling response which has some limitations (Ullsperger et al., 2010). First, participants may have become aware of an error, but might not have signaled, for example because of time pressure induced by the task. Participants had 1500 ms to signal the error, after which the next trial would start automatically. When no response was given, that corresponding trial was categorized as an unaware error. However, it could have been that in some trials participants had not yet reached a decision. This furthermore suggests that in some cases some residual error awareness may contaminate the unaware error trials (Wessel, 2012). Second, error signaling may be influenced by response bias dependent on motivational factors. When the participant is unsure about having made an error, it might induce a response bias toward not signaling an error (Wessel, 2012). Some participants may have felt that they made an error but were not confident enough to signal it while others need less information before they decide to signal the error. It cannot be excluded that motivational factors and thus different response biases of participants have influenced error signaling. The error-signaling response also has some other more general limitations. First, the error-signaling response likely entails attentional and cognitive processes additional to error awareness that are not present in the other outcomes (hits and unaware errors). Second, the error-signaling response probably interferes with post-error adjustments, which may explain the lack of a measure of behavioral adaptive control in the studies included in this dissertation. Indeed, additional analyses were performed but post-error slowing was not present in the data. Third, error awareness is not measured directly but only by introspection. Despite these limitations, this standard procedure has been extensively used in previous studies and it provides consistent modulation of the late Pe by error awareness. In addition to the use of an error signaling

response, the use of a stringent response deadline adjusted to performance of the participant is a limitation as well as an asset of the task. On the one hand, it reduces inter-individual variability and causes all participants to make a relatively balanced amount of errors, which hampers finding a difference between groups in the number of aware errors in *Chapters 2* and *4*. On the other hand, this approach causes participants to make a high amount of errors in a short period of time. Moreover, the fact that the amount of errors are relatively balanced is important for between-groups comparisons as a relatively equal amount of error trials are averaged which influences the reliability of ERP waveforms. A final limitation of this task was the confound of difficulty. Most aware errors were made in the easy condition of the No-Go trials, while most unaware errors were made in the difficult condition. In the study from *Chapter 2* enough aware errors were also made in the unaware condition, it was therefore decided to analyze only the difficult condition. However, this was not the case in the study included in *Chapter 4* and errors were therefore analyzed across conditions, making it impossible to disentangle error awareness and difficulty in this study.

Sixth, all the conclusions regarding deficient error awareness in ADHD are based on waveforms averaged across trials. If inferences are made about deficient error awareness in ADHD, this should be reflected in smaller Pe amplitudes in the ADHD group compared to control group on every trial. However, at the single-trial level, it cannot be excluded that these smaller Pe amplitudes in the ADHD group resulted from individuals with ADHD being sometimes completely aware of the error while being almost not aware of errors on other trials, which would lead to other conclusions on the underlying mechanism of deficient error awareness in ADHD. Single-trial analysis is clearly needed to shed light on this matter.

Seventh, although high-density EEG was recorded, ERPs were mostly analyzed at the midline positions. It would be interesting to apply additional analyses, such as topographical mapping analyses (Murray, Brunet, & Michel, 2008) or use mathematical transformations to gain insight into the underlying neural sources (e.g., sLORETA as in *Chapter 4* in this dissertation; Pascual-Marqui, 2002). Although estimation of source localization on the basis of EEG has extensively improved, it still has rather poor spatial resolution because activity is recorded from the scalp and therefore deeply situated

neural sources are still difficult to measure with EEG. To identify the underlying neural sources, other techniques such as fMRI are warranted.

FUTURE RESEARCH

The research findings presented in this dissertation raised several questions that may guide future research. In the following section, some suggestions for further research are formulated.

First, our findings suggest that the ERN and early Pe can be modulated by error awareness (under specific circumstances) and that the late Pe is therefore not the exclusive correlate of error awareness. How conscious processing is reflected in the correlates of error processing seems to be dependent on several methodological factors, such as the experimental paradigm used (Shalgi & Deouell, 2013; Wessel, 2012). Future research should therefore use a paradigm optimally adjusted to investigate error awareness in order to gain more insights into the functional significance of the correlates of error processing and in extension to help better understand deficient error awareness in ADHD. First, according to Geburek and colleagues (2013), this error awareness paradigm should best be a Go/No-Go task. In their meta-analysis, an effect of type of task was found, with consistent smaller Pe amplitudes in adults with ADHD in a Go/No-Go task but not in the flanker task. The crucial difference between both tasks is that in the Go/No-Go task an error is an incorrect button press when no response was required, while an error in the flanker task is a wrong response while a response was always required. Therefore, errors in the Go/No-Go task are more salient and more easily detected. These authors thus argued that the Go/No-Go task is a more ideal task to study error awareness since only in this task individuals can rely on their own covert reactions to become aware of their error. Second, in this optimal error awareness paradigm, the criticized error signaling response (Ullsperger et al., 2010) should best be replaced with a post-decision wagering procedure (Persaud, McLeod, & Cowey, 2007). In this procedure, participants have to indicate on every trial whether they were correct or made an error (accuracy judgment), followed by indicating their confidence on this accuracy judgment by betting either a small or large amount of money (confidence

judgment). Unlike the error signaling response, this procedure does not involve introspection, measures awareness directly and feels more intuitive to participants (Persaud et al., 2007). Furthermore, by asking participants to place a wager on every trial, the confound of additional attentional and cognitive processes induced by the error signaling response only on aware error trials is circumvented. By means of this post-decision wagering procedure, it was shown that the ERN amplitude is modulated by subjective confidence since a larger ERN amplitude for aware than unaware errors was observed in high confidence trials while no difference in ERN amplitude for aware and unaware errors was found in low confidence trials (Shalgi & Deouell, 2012). Interestingly, also the late Pe has recently been argued to reflect subjective confidence (Boldt & Yeung, 2015). These findings suggest shared mechanisms underlying error processing and confidence judgments, which could possibly have important implications for the functional significance of the neural correlates of error processing as well as deficient error awareness in ADHD and future research should probably focus on this promising avenue. It could furthermore help understand the puzzling finding in *Chapter 4* of an intact ERN, an impaired early Pe and normal late Pe in ADHD, as it was hypothesized that the accumulation of error evidence is more noise or blurry (as evidenced by the early Pe) in this patient group, but that they are as confident about making an error as individuals without ADHD.

Second, as previously mentioned, future research should focus on error-preceding brain activity and use single-trial analysis. This would provide valuable knowledge on the possible reasons for diminished error awareness in ADHD, which on the one hand could be the result of attentional fluctuations related to aberrant default-mode network activity or on the other hand, be due to sustained response inhibition related to abnormal activation of the rIFG.

Third, the basic skill of interoceptive awareness was found preserved in adults with ADHD. However, this does not exclude the possibility that becoming aware of bodily signals might be disrupted during other tasks or in daily life, perhaps as a result of reduced attention. It is often thought that interoceptive and exteroceptive signals use and compete for the same limited attentional resources (Vaitl, 1996). It could also be that individuals with ADHD are able to become aware of bodily signals but are not able to use the available information sufficiently, because this information is wrongly applied

or interpreted. In line with a framework developed for depression (Harshaw, 2015), it could be that cognitive and self-regulatory deficits in ADHD are products of an impaired integration of interoceptive and exteroceptive signals, which is performed by the insula (Simmons et al., 2013). It would therefore be interesting for future neuroimaging research to test this patient group in an exteroceptive task of which it is known to be dependent upon interoceptive signals (e.g., the speeded Go/No-Go task with an explicit measure of error awareness used in this dissertation) and focus on neural activity of the insula.

Fourth, further research on the conditions in which the presence of novels can have beneficial effects is required. For example, one could wonder whether this is when novels are in or out of the focus of attention. While in the four-stimulus oddball task novels are presented in the focus of attention, in daily life, when performing a task, individuals with ADHD are often distracted by novels outside the focus of attention. It is therefore important to test for this possible beneficial effect in more naturalistic settings. Future research should also try to investigate what the underlying mechanism of this possible beneficial effect is and implement manipulations that tackle this mechanism. Based on the state regulation account (van der Meere, 2005), it could be hypothesized that novels increase arousal. In addition, it was shown that ADHD is characterized by a dysfunction of stimulus weighing in ADHD, since task-irrelevant novels were processed further as task-relevant in this patient group. It would therefore be interesting to compare the processing of task-irrelevant novels and task-relevant novels in ADHD to shed more light on this impaired salience attribution in ADHD.

Fifth, although indirect evidence against a resemblance in processing of errors and targets on the one hand and errors and novels on the other hand was provided and because no firm conclusions could be drawn from the additional analyses on the processing of these stimuli across both paradigms used in this dissertation, some suggestions for future research can be formulated that would improve our understanding of the processing of salient stimuli in general and in extension in ADHD. Future research should investigate the processing of aware errors and the processing of other salient stimuli within the same paradigm instead of across paradigms and gain insight into the common underlying neural generators. Attempts have been made, for example with the hybrid error-monitoring/novelty-oddball paradigm (Wessel,

Danielmeier, Morton, & Ullsperger, 2012), but these hybrid paradigms have not used an explicit measure of error awareness. Ideally, a combination of the speeded Go/No-Go task with the explicit measure of error awareness and the four-stimulus oddball task should be made. Furthermore, errors are not only salient because they are infrequent and task-relevant, but also because they have a negative emotional valence. The processing of errors should therefore also be compared with the processing of emotional stimuli. Abnormalities in emotional processing in ADHD have indeed been reported (Herrmann et al., 2009). A five-stimulus oddball task can be applied with an emotional stimulus as a fourth infrequently presented stimulus, in agreement with previous studies (Bunzeck & Düzel, 2006; Bunzeck et al., 2007). In addition, to further test the hypothesis that the late Pe resembles a P3b evoked to the motivational significance of an error, future research should implement manipulations that have shown to reliably influence the P3b amplitude, such as the modulation of event rate.

CONCLUSION

The aim of this dissertation was to increase knowledge on the processing of errors and other salient stimuli in ADHD. The results of this dissertation show that there is indeed deficient error awareness in ADHD, at the level of the early Pe. The late Pe to aware errors was not smaller in adults with ADHD. The basic skill of interoceptive awareness, a source of error evidence shown to underlie the emergence of error awareness, was preserved in ADHD. Furthermore, evidence for disturbed processing of novels in ADHD has been provided. The findings suggest that ADHD is not characterized by an increased distractibility by novels but by a disturbance in salience attribution to novels as these stimuli were further processed as task-relevant stimuli. The processing of targets was found unimpaired in ADHD, which may relate to the context-dependent nature of this disorder. The results are not supportive of a general deficit in the processing of salient stimuli in ADHD. In conclusion, the findings in this dissertation add to the existing literature on the problems with the processing of salient stimuli (aware errors and novels) in ADHD. The findings have important methodological, theoretical and clinical implications and generate important new questions for future research.

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NEDERLANDSTALIGE SAMENVATTING

INLEIDING

Aandachtsdeficiëntie-/hyperactiviteitsstoornis

Aandachtsdeficiëntie-/hyperactiviteitsstoornis (*ADHD*) is een veelvoorkomende neurobiologische ontwikkelingsstoornis met aanvang in de kindertijd. ADHD wordt gekenmerkt door symptomen van onoplettendheid en/of hyperactiviteit/impulsiviteit in een mate die niet consistent is met het ontwikkelingsniveau. Die symptomen interfereren met het dagelijks leven en hebben een negatieve impact op het sociale, schoolse of beroepsmatig functioneren (*Diagnostic and Statistical Manual of Mental Disorders* [*DSM-5*], American Psychiatric Association [APA], 2013). ADHD persisteert vaak tot in de volwassenheid, maar vaak is er sprake van subtielere verschijningsvormen. Veel personen met ADHD hebben ook bijkomende stoornissen, zoals leerstoornissen, angst- en stemmingsstoornissen en autisme spectrum stoornissen. Tot op heden is het nog niet duidelijk wat precies de oorzaak van ADHD is, maar uit onderzoek blijkt dat genetische en omgevingsfactoren een belangrijke rol spelen in de ontwikkeling en het verloop van ADHD. Bovendien zijn er afwijkingen gevonden in de structuur en werking van diverse hersengebieden (Bernardi et al., 2012; Cortese, 2012; Kooij et al., 2010).

Verscheidene neuropsychologische theorieën van ADHD werden ontwikkeld om de gedrags- en cognitieve problemen die kenmerkend zijn voor ADHD te verklaren, waarvan drie zeer invloedrijk zijn gebleken en meermaals getoetst werden in onderzoek. De *executieve dysfunctie theorie* van ADHD (Barkley, 1997) suggereert dat ADHD te wijten is aan een inhibitieprobleem, wat vervolgens ook zorgt voor verstoringen in andere domeinen van executief functioneren. De twee andere theorieën hebben meer de nadruk gelegd op het dynamisch karakter van ADHD en proberen de contextafhankelijke prestaties in ADHD te verklaren. De *aversie voor uitstel theorie* (Sonuga-Barke, Taylor, Sembi, & Smith, 1992) stelt dat personen met ADHD gekenmerkt worden door een afkeer voor uitstel en wachten. Het *toestandsregulatiemodel van ADHD* (Sergeant, 2000; van der Meere, 2005), gebaseerd op het *cognitief energetisch model* van Sanders (1983),

postuleert dat personen met ADHD moeilijkheden hebben om hun energetische toestand aan te passen aan suboptimale omgevingsomstandigheden.

Ondanks een verschillende nadruk in ieder model, hebben de modellen gemeen dat ze ADHD beschouwen als een stoornis in zelfregulatie (Nigg, 2005). Zelfregulatie is een complex proces dat verschillende aspecten omvat: het verwerken van omgevingsvereisten, het aanhoudend monitoren van gedrag om na te gaan of dat gedrag aangepast is aan de specifieke omgeving, en het aanpassen van gedrag indien vereist (Shiels & Hawk, 2010; Shiels, Tamm, & Epstein, 2012). Een situatie waarin zelfregulatie erg van belang is, is na het maken van een fout. Het gedrag van personen met ADHD wordt gekenmerkt door een verhoogd aantal fouten op een groot aantal taken (Sergeant, Geurts, Huijbregts, Scheres, & Oosterlaan, 2003; Wiersema, Van Der Meere, & Roeyers, 2005). Uit onderzoek blijkt dat personen met ADHD problemen hebben met het aanpassen van hun gedrag na het maken van een fout, aangezien ze minder vertragen na het maken van een fout dan personen zonder ADHD (Balogh & Czobor, 2014; Shiels et al., 2012). Echter, het inadequaat aanpassen van het gedrag na het maken van de fout zou kunnen te wijten zijn aan een probleem in het verwerken van de fout (Shiels & Hawk, 2010). Foutverwerking, als een belangrijk onderdeel van monitoren van het gedrag, zou dus belangrijke inzichten kunnen verschaffen in het onaangepaste gedrag na het maken van een fout bij personen met ADHD.

Foutverwerking en foutbewustzijn

Foutverwerking wordt vaak onderzocht aan de hand van het elektro-encefalogram (EEG). Dit is een techniek met een zeer goede temporele resolutie waarbij elektrische activiteit van de hersenen wordt gemeten via elektrodes op de schedel. Wanneer het EEG wordt geregistreerd tijdens het maken van een fout of bij het verschijnen van een stimulus, worden verschillende opeenvolgende hersenpotentialen, zogenaamde *event-related potentials* (ERP's), gegenereerd die het tijdsverloop van fout- of stimulusverwerking weergeven. Voor de studie van foutverwerking wordt er gekeken naar twee belangrijke neurofysiologische correlaten, namelijk de *error-related negativity* (*ERN*) en de *error positivity* (*Pe*).

De ERN is een fronto-centrale negatieve component die wordt uitgelokt tijdens of onmiddellijk na het maken van een fout en wordt gegenereerd in de posterieure

mediale frontale cortex (pMFC; Debener et al., 2005; Dehaene, Posner, & Tucker, 1994; Falkenstein, Hohnsbein, Hoormann, & Blanke, 1991; Gehring, Goss, Coles, Meyer, & Donchin, 1993). Hoewel dit recent in twijfel werd getrokken (Shalgi & Deouell, 2013; Wessel, 2012), wordt vaak aangenomen dat de ERN de voorbewuste automatische detectie van de fout reflecteert aangezien die wordt uitgelokt zowel voor fouten die bewust zijn gedetecteerd (*bewuste fouten*) als voor fouten die niet werden opgemerkt (*onbewuste fouten*). De ERN component wordt gevolgd door de Pe, een grote positieve centro-pariëtale component die wordt uitgelokt tussen 300 en 500 ms na het maken van de fout en gegeneerd wordt in de pMFC en insula, en in posterieure cingulate en pariëtale gebieden (Dhar, Wiersema, & Pourtois, 2011; Klein et al., 2007; O'Connell et al., 2007). Hoewel de functionele betekenis van deze component nog niet volledig duidelijk is, wordt de Pe beschouwd als de bewuste verwerking van de fout aangezien deze component enkel wordt teweeggebracht bij bewuste fouten (Overbeek, Nieuwenhuis, & Ridderinkhof, 2005). Van belang is dat de Pe soms bestaat uit twee opeenvolgende en spatiotemporeel te onderscheiden positieve componenten en dat de bovengenoemde Pe verwijst naar de zogenaamde late Pe. De vroege Pe daarentegen is een meer fronto-centrale component die onmiddellijk na de ERN wordt opgewekt en waarvan wordt gedacht dat die functionele gelijkenissen heeft met de ERN (Debener et al., 2005; Luu, Tucker, & Makeig, 2004; Van Veen & Carter, 2002), ondanks het feit dat beide componenten gekenmerkt worden door verschillende topografieën (Arbel & Donchin, 2009; Endrass, Klawohn, Preuss, & Kathmann, 2012).

De *accumulating evidence account* (Ullsperger, Harsay, Wessel, & Ridderinkhof, 2010) is een theorie die probeert te verklaren waarom sommige fouten niet worden opgemerkt terwijl andere fouten bewust worden gedetecteerd. Volgens deze theorie komen er na het maken van een fout allerlei informatiebronnen over de fout beschikbaar op verschillende tijdsstippen en zullen die informatiebronnen beïnvloeden of een fout bewust wordt gedetecteerd of niet. Aangezien de ERN een vroeg correlaat van foutverwerking is, wordt gedacht dat die enkel beïnvloed zal worden door informatiebronnen die vroeg beschikbaar zijn na de fout. Foutbewustzijn zal ontstaan indien die gezamenlijke informatie over de fout sterk genoeg is en wordt dus verwacht voornamelijk beïnvloed te worden door informatiebronnen over de fout die later beschikbaar zijn. Aangezien de late Pe een laat correlaat is van foutverwerking en wordt

beschouwd als het neuraal correlaat van foutbewustzijn, wordt ook verwacht dat de Pe voornamelijk beïnvloed zal worden door informatiebronnen over de fout die later beschikbaar zijn. Echter, die assumpties van de accumulating evidence account (Ullsperger et al., 2010) werden nog nooit onderzocht en gevalideerd. In dit proefschrift werden twee informatiebronnen over de fout onderzocht die relatief laat beschikbaar zijn na het maken van de fout en waarvan dus wordt gedacht dat ze voornamelijk de late Pe zullen beïnvloeden (*Hoofdstuk 2*). Enerzijds werd gekeken naar visueel sensorische feedback, waaronder het zien van de responsvinger die op de responsknop duwt, wordt verstaan. Anderzijds werd interoceptief bewustzijn onderzocht, wat refereert aan het bewustzijn van autonome lichaamssignalen (Garfinkel, Seth, Barrett, Suzuki, & Critchley, 2015).

Voorgaand onderzoek heeft al eerder evidentie aangereikt voor een link tussen interoceptief bewustzijn en de late Pe (Sueyoshi, Sugimoto, Katayama, & Fukushima, 2014). Bovendien werd al meermaals aangetoond dat interoceptief bewustzijn van belang is voor allerlei cognitieve functies die belangrijk zijn voor zelfregulatie en die ook verstoord blijken te zijn in ADHD (Balogh & Czobor, 2014; Herbert, Pollatos, & Schandry, 2007; Herrmann et al., 2009; Sueyoshi et al., 2014). Verder wordt ook door het toestandsregulatiemodel (Sergeant, 2000; van der Meere, 2005) het belang benadrukt van het monitoren van de toestand van het lichaam voor zelfregulatie. Tot op heden heeft nog geen enkele studie de vaardigheid om bewust te worden van autonome lichaamssignalen bij personen met ADHD onderzocht, ondanks het belang van deze vaardigheid voor zelfregulatie in ADHD. Omwille van deze redenen werd in dit proefschrift interoceptief bewustzijn in volwassenen met ADHD onderzocht (*Hoofdstuk 3*).

Evidentie voor abnormaal foutbewustzijn in kinderen en volwassenen met ADHD is tot op heden inconsistent (Geburek, Rist, Gediga, Stroux, & Pedersen, 2013; Shiels & Hawk, 2010). Bovendien maakten de meeste voorgaande studies geen gebruik van een expliciete maat van foutbewustzijn. In taken die echt peilen naar foutbewustzijn worden personen expliciet gevraagd of ze gemerkt hebben dat ze een fout hebben gemaakt en of ze die fout kunnen signaleren door bijvoorbeeld op een extra responsknop te drukken die niet gerelateerd is aan de hoofdtaak. Enkel op deze manier kunnen (ERP's uitgelokt door) bewuste fouten expliciet worden gecontrasteerd met (ERP's uitgelokt door)

onbewuste fouten en enkel zo kan abnormaal foutbewustzijn in ADHD ondubbelzinnig worden aangetoond. Tot op heden heeft maar één studie foutbewustzijn bij volwassen met ADHD onderzocht in een taak die gebruik maakte van een expliciete maat van foutenbewustzijn (O'Connell et al., 2009). Deze studie vond evidentie voor verminderd foutbewustzijn bij volwassenen met ADHD, aangezien algemeen meer fouten, maar minder vaak bewuste fouten, en kleinere late Pe amplitudes voor bewuste fouten in volwassenen met ADHD werden gevonden. Bovendien werd een normale ERN voor zowel bewuste als onbewuste fouten in ADHD gevonden en algemeen kleinere amplitudes van de vroege Pe voor zowel bewuste en onbewuste fouten als correcte responsen. Aangezien replicatie van deze bevindingen nodig is om de hypothese van verminderd foutbewustzijn in ADHD kracht bij te zetten, werd in dit proefschrift foutbewustzijn bij volwassenen met ADHD onderzocht met behulp van een taak waarin een expliciete maat van foutbewustzijn werd opgenomen (*Hoofdstuk 4*).

Verwerking van andere saillante stimuli

Een bewuste fout kan beschouwd worden als een saillante stimulus, aangezien die fout infrequent voorkomt en taakrelevant is. *Saillantie* wordt gedefineerd als de motivationele relevantie van de stimulus voor de waarnemer bepaald door de *bottom-up* karakteristieke kenmerken van de stimulus en/of door *top-down* processen zoals verwachtingen en doelen van de waarnemer (Cunningham & Brosch, 2012; Uddin, 2014). Een stimulus kan dus saillant zijn omwille van verschillende redenen, zoals bijvoorbeeld de gedragsrelevantie, de emotionele valentie, de infrequentie van de stimulus. Het is aangetoond dat het saillantie netwerk, met de anterieure insula als centrale hub, actief is tijdens het verwerken van allerlei saillante stimuli (Menon & Uddin, 2010; Seeley et al., 2007) en dat dit netwerk sterk overlapt met de gebieden die actief zijn tijdens foutverwerking (Ullsperger et al., 2010).

Naast fouten zijn twee andere soorten van saillante stimuli vaak onderzocht, namelijk targets en novels. In een oddball taak worden taakrelevante targets en taakirrelevante novels infrequent gepresenteerd tijdens een serie van frequent gepresenteerde standard stimuli. Twee specifieke varianten van de P3 component worden uitgelokt voor deze stimuli, namelijk de *P3b* voor targets en de *novelty P3* voor novels. De P3b is een pariëtale positieve component die uitgelokt wordt tussen 300 en

600 ms na de stimulus en die de mate van top-down allocatie van aandacht aan de stimulus reflecteert (Kok, 2001), terwijl de novelty P3 een (fronto-)centrale positieve component is die teweeggebracht wordt tussen 300 en 400 ms na de stimulus en waarvan gedacht wordt dat die de bottom-up allocatie van aandacht aan afleidende taakirrelevante stimuli reflecteert (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2007).

Structurele afwijkingen van de insula (Lopez-Larson, King, Terry, McGlade, & Yurgelun-Todd, 2012) alsook abnormale functionele connectiviteit tussen het saillantie netwerk en andere netwerken (Sidlauskaite, Sonuga-Barke, Roeyers, & Wiersema, 2015) werden eerder gerapporteerd in ADHD. Bovendien vertonen personen met ADHD problemen met het verwerken van verschillende soorten saillante stimuli, zoals (bewuste) fouten (Balogh & Czobor, 2014; Geburek et al., 2013), beloningen (Luman, Tripp, & Scheres, 2010), emotionele stimuli (Herrmann et al., 2009), targets (Johnstone, Barry, & Clarke, 2013) en novels (Gumenyuk et al., 2005; Marzinzik et al., 2012; van Mourik, Oosterlaan, Heslenfeld, Konig, & Sergeant, 2007). Deze bevindingen suggereren een algemeen probleem met het verwerken van saillante stimuli in ADHD. Met betrekking tot het verwerken van targets werd in de meeste studies een kleinere P3b amplitude voor targets gevonden in ADHD (Johnstone, Barry, & Clarke, 2013; Szuromi, Czobor, Komlósi, & Bitter, 2011, maar zie Wiersema, van der Meere, Roeyers, Van Coster, & Baeyens, 2006). Onderzoek naar het verwerken van novels in ADHD is minder consistent, met studies die een grotere (Gumenyuk et al., 2005; van Mourik et al., 2007) of een normale novelty P3 (Jonkman et al., 2000) voor novels vonden in kinderen met ADHD. Er is weinig onderzoek uitgevoerd naar het verwerken van novels bij volwassenen met ADHD, maar dat onderzoek suggereert abnormale verwerking van novels (Marzinzik et al., 2012). Belangrijk om op te merken is dat de conceptualisatie van de novel sterk verschilt tussen studies, aangezien die novel betekenisvol of betekenisloos kan zijn, visueel eenvoudig of complex kan zijn, en herhaaldelijk kan worden gepresenteerd of net uniek is bij iedere presentatie. Volgens Zaehle et al. (2013) is een zuivere novel uniek bij iedere presentatie en wordt die voor de eerste keer waargenomen, terwijl een afwijkende non-target een reeds gekende, infrequent en herhaaldelijk gepresenteerde stimulus is. Er is dus nood aan meer onderzoek dat het verwerken van saillante stimuli in ADHD onder de loep neemt, waarbij verschillende soorten saillante stimuli beter worden afgebakend (*Hoofdstuk 5*).

DOELSTELLINGEN VAN HET DOCTORAATSPROEFSCHRIFT

Tot op heden is het nog niet duidelijk hoe sommige fouten onopgemerkt blijven, terwijl andere bewust worden gedetecteerd. De accumulating evidence account (Ullsperger et al., 2010) heeft een theoretisch kader rond het ontstaan van foutbewustzijn aangereikt, maar de assumpties met betrekking tot de informatiebronnen over de fout, die onderliggend zouden zijn aan foutbewustzijn, werden nog niet getest. Het eerste doel van dit proefschrift was dus het testen van die assumpties in een groep normaal ontwikkelde volwassenen aan de hand van een snelle Go/No-Go taak waarin een expliciete maat van foutbewustzijn was voorzien om meer inzicht te krijgen in de processen die leiden tot foutbewustzijn. Meer specifiek, met behulp van ERP's, werden twee informatiebronnen onderzocht, namelijk visueel sensorische feedback en interoceptief bewustzijn, waarvan wordt verondersteld dat die relatief laat beschikbaar worden na het maken van de fout en voornamelijk de late Pe zullen beïnvloeden. De invloed van visueel sensorische feedback op het ontstaan van foutbewustzijn werd onderzocht door het manipuleren van de zichtbaarheid van de responshand in een *between-subjects design*. Interoceptief bewustzijn werd nagegaan in een hartslag perceptie taak waarin proefpersonen hun eigen hartslagen moeten tellen in drie verschillende intervallen.

De vaardigheid om bewust te worden van interne autonome lichaamssignalen (meer specifiek hartslagen) werd verondersteld van belang te zijn voor foutbewustzijn en voor het monitoren van de lichaamstoestand (toestandsregulatiemodel). Daarom was het tweede doel van dit proefschrift om interoceptief bewustzijn in volwassenen met ADHD te onderzoeken. Volwassenen met en zonder ADHD voerden een objectieve hartslag perceptie taak uit en vervolledigden een subjectieve maat (vragenlijst) van interoceptief bewustzijn.

Verder, aangezien evidentie voor verminderd foutbewustzijn in ADHD inconsistent is (Geburek et al., 2013; Shiels & Hawk, 2010) en maar één studie tot op heden gebruik heeft gemaakt van een expliciete maat van foutbewustzijn (O'Connell et al., 2009), was het derde doel van dit proefschrift om aan de hand van ERP's foutbewustzijn bij volwassenen met ADHD te onderzoeken in een paradigma waarin een expliciete maat van foutbewustzijn was voorzien. Volwassenen met en zonder ADHD voerden een snelle

Go/No-Go taak uit waarin ze werden gevraagd om een bewust gedetecteerde fout te signaleren door het drukken op een extra responsknop. Aanvullende bronlokalisatie analyses werden uitgevoerd om de mechanismen onderliggend aan verminderd foutbewustzijn in ADHD in kaart te brengen.

Ten slotte, personen met ADHD vertonen niet enkel moeilijkheden in het verwerken van fouten maar ook in het verwerken van andere saillante stimuli, wat een algemeen probleem met het verwerken van saillante stimuli in ADHD suggereert. Het vierde doel van het proefschrift was dus om te onderzoeken of personen met ADHD gekenmerkt worden door abnormale verwerking van targets en novels. Volwassenen met en zonder ADHD voerden een vier-stimulus oddball taak uit waarin taakrelevante targets en taakirrelevante non-targets en novels infrequent werden gepresenteerd in een reeks van frequent gepresenteerde standards. Door het toepassen van specifieke contrasten werden verschillende soorten saillantie onderzocht, namelijk *deviance*, *targetness* en *novelty*.

OVERZICHT EN BESPREKING VAN DE BELANGRIJKSTE BEVINDINGEN

Foutverwerking

Evidentie voor de accumulating evidence account. In overeenstemming met de assumpties van de accumulating evidence account (Ullsperger et al., 2010), hadden zowel visueel sensorische feedback als interoceptief bewustzijn een invloed op het ontstaan van foutbewustzijn en op de late Pe. De bevindingen rond visuele sensorische feedback waren echter niet in overeenstemming met onze verwachtingen, aangezien het effect van bewustzijn (i.e., verschil tussen bewuste en onbewuste fouten) groter was als visuele sensorische feedback van de responshand niet beschikbaar was. Dit kon echter verklaard worden door de observatie dat de ERN gemoduleerd werd door foutbewustzijn, maar enkel als visuele sensorische feedback beschikbaar was. In dit geval bleek foutbewustzijn blijkbaar later te ontstaan dan wanneer de responshand niet zichtbaar was en dit reflecteerde zich in een grotere late Pe amplitude wanneer visuele sensorische feedback van de responshand niet beschikbaar was. Deze bevindingen zijn

niet in overeenkomst met de assumptie van de accumulating evidence account (Ullsperger et al., 2010), waarin wordt gesteld dat de ERN enkel beïnvloed wordt door informatiebronnen die vroeg beschikbaar worden na het maken van de fout. De bevindingen ondersteunen echter wel het idee dat foutbewustzijn het resultaat is van een accumulatie van informatiebronnen over de fout en dat foutbewustzijn later ontstaat wanneer een belangrijke informatiebron niet beschikbaar is.

Er werd een positieve correlatie tussen de gemiddelde hartslag perceptie score en de amplitude van de late Pe gevonden. Deze bevinding is in overeenkomst met een studie die reeds een link tussen interoceptief bewustzijn en de late Pe had getoond (Sueyoshi et al., 2014). Deze studie maakte echter geen gebruik van een expliciete maat van foutbewustzijn, wat noodzakelijk is om interoceptief bewustzijn ondubbelzinnig aan foutbewustzijn en dus de late Pe te koppelen. In onze studie werd bovendien enkel een link met de late Pe en niet met de ERN gevonden, wat de assumptie van de accumulating evidence account (Ullsperger et al., 2010) ondersteunt dat informatiebronnen over de fout die relatief laat beschikbaar worden na het maken van de fout voornamelijk late correlaten van foutverwerking beïnvloeden, met name de late Pe. Samengevat, deze bevindingen bieden sterke ondersteuning voor de assumpties van de accumulating evidence account (Ullsperger et al., 2010) die stellen dat verschillende informatiebronnen over de fout beschikbaar worden op verschillende momenten na het maken van de fout en op een bepaald moment het ontstaan van foutbewustzijn beïnvloeden. Meer specifiek, het werd aangetoond dat het bewust worden van fouten afhankelijk is van visuele sensorische feedback van de responshand en de vaardigheid om bewust te worden van lichaamssignalen.

Intact interoceptief bewustzijn in ADHD. Volwassenen met en zonder ADHD verschilden niet voor de objectieve of subjectieve maat van interoceptief bewustzijn, wat intact interoceptief bewustzijn in ADHD suggereert. Het belang van interoceptief bewustzijn voor het ontstaan van foutbewustzijn werd reeds eerder aangetoond (Sueyoshi et al., 2014) en het monitoren van de lichaamstoestand werd ook eerder verondersteld van belang te zijn voor effectieve toestandsregulatie en dus zelfregulatie (Sergeant, 2000; van der Meere, 2005). Daarom suggereren deze bevindingen dat verminderd foutbewustzijn in ADHD en breder, het probleem met reguleren van de

toestand en zelfregulatie in ADHD, niet te wijten is aan een onvermogen om bewust te worden van lichaamssignalen.

Verminderd foutbewustzijn in ADHD. Volwassenen met ADHD signaleerden evenveel bewuste fouten als volwassenen zonder ADHD, wat niet in overeenkomst is met de verwachtingen en de studie van O'Connell et al. (2009). In tegenstelling tot de bevindingen van de meta-analyse over foutverwerking in volwassenen met ADHD (Geburek et al., 2013), maar in overeenstemming met de studie van O'Connell et al. (2009) die gebruik maakte van een expliciete maat van foutbewustzijn, was de ERN voor bewuste fouten niet kleiner in ADHD. In strijd met de bevindingen van O'Connell et al. (2009), was de late Pe voor bewuste fouten eveneens niet kleiner in ADHD, wat dan wel weer in overeenkomst is met de bevinding dat interoceptief bewustzijn intact was in volwassenen met ADHD. Er werd echter een kleiner effect van bewustzijn gevonden voor de vroege Pe in volwassenen met ADHD. In de studie van O'Connell et al. (2009) werd ook een kleinere vroege Pe in ADHD gevonden, maar onafhankelijk van bewustzijn aangezien deze vroege Pe kleiner was voor zowel bewuste en onbewuste fouten als correcte responsen. Een kleinere vroege Pe voor fouten werd ook eerder gevonden in een studie met kinderen met ADHD maar die studie maakte geen gebruik van een expliciete maat van foutbewustzijn (Van De Voorde, Roeyers, & Wiersema, 2010). Bronlokalisatie analyses toonden verder aan dat dit kleiner effect van bewustzijn op het niveau van de vroege Pe in ADHD gepaard ging met meer activatie van de rechter inferieure frontale gyrus in de ADHD groep in vergelijking met de controle groep. Voor de ADHD groep was deze activatie bovendien negatief gecorreleerd met het percentage bewuste fouten. Dit gebied werd eerder gerelateerd aan respons inhibitie en werd consistent verstoord bevonden in ADHD (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Lei et al., 2015; Rubia, 2011). Hoewel meer onderzoek nodig is om na te gaan hoe de toegenomen activatie van de rechter inferieure frontale gyrus gerelateerd is aan verminderd foutbewustzijn in ADHD, suggereert deze bevinding dat een gebied dat van belang is voor respons inhibitie nog steeds geactiveerd is na het maken van de fout in de ADHD groep. Algemeen bieden de bevindingen ondersteuning voor verminderd foutbewustzijn bij volwassenen met ADHD, met name op het niveau van de vroege Pe.

Verwerking van andere saillante stimuli

Evidentie voor een normale verwerking van non-targets werd aangereikt en deze bevinding benadrukt nogmaals het belang van het maken van een duidelijk onderscheid tussen afwijkende non-targets en zuivere novels. In tegenstelling tot een groot aantal vorige studies (Johnstone et al., 2013; Marzinzik et al., 2012; Szuromi et al., 2011) werd geen evidentie gevonden voor een abnormale verwerking van targets in ADHD aangezien de P3b voor targets niet kleiner was bij volwassenen met ADHD dan zonder ADHD. Dit stemt overeen met een aantal studies die ook een normale P3b in ADHD hebben gerapporteerd, in het geval van een snelle presentatie van stimuli maar niet in het geval van een trage presentatie (Wiersema, van der Meere, Antrop, & Roeyers, 2006; Wiersema, van der Meere, Roeyers, Van Coster, et al., 2006). Deze bevindingen alsook de bevindingen in dit proefschrift suggereren dat taakprestatie en in het verlengde een probleem met top-down allocatie van aandacht in ADHD mogelijks contextafhankelijk is. Deze hypothese is in overeenstemming met het huidige idee dat ADHD een contextafhankelijke stoornis van zelfregulatie is, wat wordt ondersteund door neuropsychologische theorieën zoals het toestandsregulatiemodel (Sergeant, 2000; van der Meere, 2005).

De bevindingen suggereren dat volwassenen met ADHD niet makkelijker afleidbaar zijn door taakirrelevante novels aangezien een normale novelty P3 voor novels werd gevonden in deze groep. Deze bevinding voegt toe aan de inconsistenties in de literatuur met betrekking tot deze component (Gumenyuk et al., 2005; Jonkman et al., 2000; Marzinzik et al., 2012; van Mourik et al., 2007). Er werd echter wel evidentie gevonden voor abnormale allocatie van aandacht in ADHD, aangezien een grotere P3b voor novels werd geobserveerd in ADHD. Deze bevinding impliceert dat ADHD gekenmerkt wordt door een verstoorde attributie van saillantie aan novels, aangezien deze taakirrelevante novels verder verwerkt werden als taakrelevante stimuli. Verstoorde verwerking van novels op het niveau van de P3b in ADHD werd al eerder gerapporteerd (Marzinzik et al., 2012), maar meer onderzoek naar de verwerking van novels in volwassenen met ADHD is nodig.

De bevindingen uit de verschillende hoofdstukken in dit proefschrift bieden indirecte evidentie tegen de hypothese van een algemeen probleem met het verwerken van saillante informatie in ADHD. Een normale verwerking van non-targets en targets

werd geobserveerd terwijl het verwerken van bewuste fouten en novels verstoord was in ADHD.

IMPLICATIES

Theoretische en methodologische implicaties

De bevindingen bieden ondersteuning aan verstoord foutbewustzijn en intact interoceptief bewustzijn in ADHD. Dit impliceert dat verstoord foutbewustzijn in ADHD waarschijnlijk niet te verklaren valt door een onvermogen om bewust te worden van lichaamssignalen. De vraag blijft dus hoe dit verminderd foutbewustzijn in ADHD kan worden verklaard. Enerzijds kan het gerelateerd zijn aan processen die zich al voordoen voor het maken van de fout. Er is veel evidentie dat fouten worden voorafgegaan door afwijkende hersenactiviteit en dat kortstondige aandachtsfluctuaties, die waarschijnlijk voortkomen uit verminderde deactivatie van het default-mode netwerk, gerelateerd zijn aan het nadien maken van een fout (Cavanagh, Cohen, & Allen, 2009; Eichele, Juvodden, Ullsperger, & Eichele, 2010; Mazaheri, DiQuattro, Bengson, & Geng, 2011; Ridderinkhof, Nieuwenhuis, & Bashore, 2003). Het belang van verstoorde activiteit van het default-mode netwerk in ADHD werd reeds eerder benadrukt in de *default-mode interferentie hypothese* (Sonuga-Barke & Castellanos, 2007) en evidentie voor verstoorde functionele connectiviteit in het default-mode netwerk in ADHD werd reeds eerder aangebracht (Sidlauskaite et al., 2015). Hoewel toekomstig onderzoek nodig is om de hypothese te bevestigen, zou het dus kunnen dat bewuste en onbewuste fouten in ADHD voorafgegaan worden door verschillende patronen van verstoorde hersenactiviteit en dat dit verminderd foutbewustzijn in ADHD verklaart. Anderzijds kan het verminderde foutbewustzijn in ADHD gerelateerd zijn aan de geobserveerde verhoogde activatie van de rechter inferieure frontale gyrus. Dit impliceert volgehouden inhibitie van de foute respons, maar het is nog niet duidelijk of deze volgehouden inhibitie in ADHD leidt tot verminderd foutbewustzijn of verminderd foutbewustzijn in ADHD leidt tot volgehouden inhibitie. Meer onderzoek is nodig om de richting van dit effect na te gaan en dit zou bijdragen tot een mogelijkse verklaring van verstoord foutbewustzijn in ADHD in termen van een inhibitieprobleem, wat in overeenstemming zou zijn met de *executieve dysfunctie theorie* (Barkley, 1997).

De bevinding dat interoceptief bewustzijn in ADHD intact is, heeft implicaties voor het toestandsregulatiemodel (van der Meere, 2005) aangezien het impliceert dat de problemen met zelfregulatie in ADHD niet te wijten zijn aan een onvermogen om bewust te worden van lichaamssignalen. De vraag wat nu eigenlijk leidt tot die problemen met zelfregulatie in ADHD moet dus nog worden beantwoord. Het is nog steeds mogelijk dat personen met ADHD moeilijkheden hebben met het aanpassen van hun energetische toestand om te compenseren voor suboptimale omgevingsomstandigheden, ondanks de correcte evaluatie van de lichaamstoestand. Verder zou het ook kunnen dat de problemen met zelfregulatie in ADHD gerelateerd zijn aan een algemeen veranderde motivationele attitude, zoals gepostuleerd door bijvoorbeeld de aversie voor uitstel theorie (Sonuga-Barke et al., 1992). Evidentie voor motivationele problemen en problemen met het verwerken van beloningsstimuli in ADHD werd eerder gevonden (Luman et al., 2010). Ten slotte zou het kunnen dat problemen met zelfregulatie in ADHD gerelateerd zijn aan een probleem met het verwerken van feedback over de prestatie. Sommige studies bieden ondersteuning voor het idee dat personen met ADHD feedback minder goed verwerken doordat ze een kleinere feedback-related negativity (FRN), wat de feedback-variant van de ERN is, observeren in deze groep (Groen, Tucha, Wijers, & Althaus, 2013; Van Meel, Heslenfeld, Oosterlaan, Luman, & Sergeant, 2011; Van Meel, Oosterlaan, Heslenfeld, & Sergeant, 2005).

Klinische implicaties

De bevinding in dit proefschrift alsook de eerdere evidentie van verminderd foutbewustzijn in kinderen en volwassenen met ADHD (Geburek et al., 2013; O'Connell et al., 2009; Shiels & Hawk, 2010) suggereren dat een probleem met foutbewustzijn een belangrijk aspect is van de stoornis, reeds aanwezig in de kindertijd en persisterend in de volwassenheid. Omdat het bewust worden van fouten van groot belang is voor flexibele gedragsaanpassingen en voor het leren van het vermijden van fout gedrag op lange termijn, zou het onderdeel kunnen uitmaken van interventie. Tot op heden is er echter nog maar weinig geweten over de impact van behandelingsprogramma's op verstoord foutbewustzijn (Sonuga-Barke et al., 2013) en verder onderzoek moet zich richten op het nut van interventies voor verminderd foutbewustzijn in ADHD.

In het dagelijks leven is het belangrijk om snel een onderscheid te kunnen maken tussen novels die niet verder verwerkt moeten worden en novels waarop wel dient gereageerd te worden. Blijkbaar hebben personen met ADHD moeite om dit onderscheid te maken, aangezien de bevindingen suggereren dat volwassen met ADHD taakirrelevante novels verder verwerken als taakrelevante stimuli. Bovendien is het eerder aangetoond dat de presentatie van novels soms een nadelig (Gumenyuk et al., 2005) en soms een gunstig (Tegelbeckers et al., 2016; van Mourik et al., 2007) effect kan hebben op de taakprestatie van personen met ADHD. Aangezien de bevindingen suggereren dat personen met ADHD problemen hebben met het verwerken van novels, dringt de vraag zich op wanneer de presentatie van novels een voordelig of nadelig effect zal hebben op de taakprestatie. Het identificeren van die voordelige of nadelige omstandigheden in toekomstig onderzoek is van belang voor het optimaliseren van de behandeling, opdat optimale omstandigheden voor taakprestatie kunnen worden gecreëerd door de klas- of werkomgeving van de persoon met ADHD aan te passen.

Daaraan gerelateerd wezen de bevindingen op het belang van de context voor de taakprestatie in ADHD, aangezien een normale P3b voor targets in volwassenen met ADHD werd geobserveerd. Het zou kunnen dat dit te wijten is aan de stimulerende aard van de vier-stimulus oddball taak. Het werd eerder aangetoond dat externe stimulatie, zoals een snelle presentatie van stimuli, de presentatie van witte ruis en de presentatie van novels, gunstige effecten kan hebben op de prestatie in ADHD (Börger & van der Meere, 2000; Tegelbeckers et al., 2016; van Mourik et al., 2007; Wiersema, van der Meere, Antrop, et al., 2006; Wiersema, van der Meere, Van Coster et al., 2006). Toekomstig onderzoek dient na te gaan of de contextafhankelijke verwerking van taakrelevante stimuli in ADHD beïnvloed kan worden door externe stimulatie met het uiteindelijke doel om klinische interventies te optimaliseren door de omstandigheden te identificeren waarin externe stimulatie de taakprestatie in ADHD verbetert.

CONCLUSIE

De doelstelling van dit proefschrift was om meer kennis te vergaren over het verwerken van fouten en andere saillante stimuli in ADHD. De bevindingen in dit proefschrift tonen dat er verminderd foutbewustzijn is in ADHD, maar op het niveau van de vroege Pe. De amplitude van de late Pe voor bewuste fouten was niet kleiner in volwassenen met ADHD. De basisvaardigheid van interoceptief bewustzijn, een informatiebron waarvan het werd aangetoond dat die onderliggend is aan het ontstaan van foutbewustzijn, was intact in ADHD. Verder werd evidentie gevonden voor een verstoorde verwerking van novels in ADHD. De bevindingen suggereren echter dat volwassenen met ADHD niet makkelijker worden afgeleid door novels, maar dat ADHD gekenmerkt wordt door een verstoorde attributie van saillantie aan novels aangezien deze taakirrelevante stimuli verder verwerkt werden als taakrelevante stimuli. Een normale verwerking van targets in ADHD werd gevonden, wat mogelijks kan gerelateerd worden aan de contextafhankelijke aard van de stoornis. De bevindingen ondersteunen niet de hypothese van een algemeen probleem met het verwerken van saillantie in ADHD. Ter besluit, de bevindingen in dit proefschrift dragen bij tot de bestaande literatuur rond de problemen in de verwerking van saillante stimuli (bewuste fouten en novels) in ADHD. De bevindingen hebben belangrijke theoretische, methodologische en klinische implicaties en genereren nieuwe relevante vragen voor toekomstig onderzoek.

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DATA STORAGE FACT SHEET CHAPTER 2

Name/identifier study: Chapter 2, Sensory feedback & interoceptive awareness
Author: Elke Godefroid
Date: 09/06/2016

1. Contact details
==========

1a. Main researcher

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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:

Godefroid, E., Pourtois, G., & Wiersema, J. R. (2016). Joint effects of sensory feedback and interoceptive awareness on conscious error detection: Evidence from event related potentials. *Biological Psychology*, *114*, 49-60. doi: 10.1016/j.biopsycho.2015.12.005

Chapter 2. Joint effects of sensory feedback and interoceptive awareness on conscious error detection: Evidence from event-related potentials.

* Which datasets in that publication does this sheet apply to?:

All datasets reported in this publication/chapter of the doctoral dissertation

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- [x] responsible ZAP
- [ ] all members of the research group
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- [ ] other (specify): ...

3b. Other files

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* Which other files have been stored?

- [x] file(s) describing the transition from raw data to reported results. Specify: Data_sensory feedback & interoceptive awareness
- [x] file(s) containing processed data. Specify: Individual Subjects History files (brain vision analyzer format: e.g., pp1.hfinf2, pp1.ehst2; pp2.hfinf2, pp2.ehst2; pp301.hfinf2, pp301.ehst2; pp302.hfinf2, pp302.ehst2, etc.) + .xls files of single subject behavioral data (pivot tables)
- [x] file(s) containing analyses. Specify: Extracted values from eeg data and imported in SPSS. SPSS files + SPSS output & syntax
- [x] files(s) containing information about informed consent
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DATA STORAGE FACT SHEET CHAPTER 3

Name/identifier study: Chapter 3, Interoceptive awareness in ADHD
Author: Elke Godefroid
Date: 09/06/2016

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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:
Chapter 3. Interoceptive awareness in ADHD.

* Which datasets in that publication does this sheet apply to?:
All the datasets reported in this chapter of the doctoral dissertation

3. Information about the files that have been stored
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3a. Raw data
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 - [x] research group file server
 - [x] other (specify): external hard drive

* Who has direct access to the raw data (i.e., without intervention of another person)?
 - [x] main researcher
 - [x] responsible ZAP
 - [ ] all members of the research group
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3b. Other files

---

* Which other files have been stored?
 - [x] file(s) describing the transition from raw data to reported results. Specify: Data_interoceptive awareness & ADHD
 - [x] file(s) containing processed data. Specify: Individual Subjects History files (brain vision analyzer format: e.g., pp201.hfinf2, pp201.ehst2; pp202.hfinf2, pp202.ehst2, etc.) + .xls files of single subject behavioral data (pivot tables)
 - [x] file(s) containing analyses. Specify: Extracted values from eeg data and imported in SPSS. SPSS files + SPSS output & syntax
 - [x] files(s) containing information about informed consent
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DATA STORAGE FACT SHEET CHAPTER 4

Name/identifier study: Chapter 4, Error awareness in ADHD
Author: Elke Godefroid
Date: 09/06/2016

1. Contact details
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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:
Chapter 4. Event-related brain potentials reveal the locus of abnormal error awareness in ADHD.

* Which datasets in that publication does this sheet apply to?:
All the datasets reported in this chapter of the doctoral dissertation

3. Information about the files that have been stored
==========

3a. Raw data
---

* Have the raw data been stored by the main researcher? [x] YES / [ ] NO

If NO, please justify:

* On which platform are the raw data stored?
 - [ ] researcher PC
 - [x] research group file server
 - [x] other (specify): external hard drive

* Who has direct access to the raw data (i.e., without intervention of another person)?
 - [x] main researcher
 - [x] responsible ZAP
 - [ ] all members of the research group
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 - [ ] other (specify):

3b. Other files

---

* Which other files have been stored?
 - [x] file(s) describing the transition from raw data to reported results. Specify: ata_error awareness & ADHD
 - [x] file(s) containing processed data. Specify: Individual Subjects History files (brain vision analyzer format: e.g., pp201.hfinf2, pp201.ehst2; pp202.hfinf2, pp202.ehst2, etc.) + .xls files of single subject behavioral data (pivot tables)
 - [x] file(s) containing analyses. Specify: Extracted values from eeg data and imported in SPSS. SPSS files + SPSS output & syntax
 - [x] files(s) containing information about informed consent: a blank copy is saved on my PC
 - [ ] a file specifying legal and ethical provisions
 - [ ] file(s) that describe the content of the stored files and how this content should be interpreted. Specify: ...
 - [ ] other files. Specify: ...

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DATA STORAGE FACT SHEET CHAPTER 5

Name/identifier study: Chapter 5, Oddball ADHD
Author: Elke Godefroid
Date: 09/06/2016

1. Contact details
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1a. Main researcher

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1b. Responsible Staff Member (ZAP)

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2. Information about the datasets to which this sheet applies
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* Reference of the publication in which the datasets are reported:
Chapter 5. Impaired processing of task-irrelevant salient information in adults with ADHD: Evidence from event-related potentials.

* Which datasets in that publication does this sheet apply to?:
All the datasets reported in this chapter of the doctoral dissertation

3. Information about the files that have been stored
==========

3a. Raw data
---

* Have the raw data been stored by the main researcher? [x] YES / [ ] NO

If NO, please justify:

* On which platform are the raw data stored?
 - [ ] researcher PC
 - [x] research group file server
 - [x] other (specify): external hard drive

* Who has direct access to the raw data (i.e., without intervention of another person)?
 - [x] main researcher
 - [x] responsible ZAP
 - [ ] all members of the research group
 - [ ] all members of UGent
 - [x] other (specify): all members of the research group conducting EEG research

3b. Other files

---

* Which other files have been stored?
 - [x] file(s) describing the transition from raw data to reported results. Specify: Data_oddball & ADHD
 - [x] file(s) containing processed data. Specify: Individual Subjects History files (brain vision analyzer format: e.g., pp201.hfinf2, pp201.ehst2; pp202.hfinf2, pp202.ehst2, etc.) + .xls files of single subject behavioral data (pivot tables)
 - [x] file(s) containing analyses. Specify: Extracted values from eeg data and imported in SPSS. SPSS files + SPSS output & syntax
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DATA STORAGE FACT SHEET GENERAL DISCUSSION

Name/identifier study: Chapter 6, General discussion
Author: Elke Godefroid
Date: 09/06/2016

1. Contact details
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1b. Responsible Staff Member (ZAP)

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* Reference of the publication in which the datasets are reported:
Chapter 6. General discussion.

* Which datasets in that publication does this sheet apply to?:
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3. Information about the files that have been stored
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3a. Raw data
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* Have the raw data been stored by the main researcher? [x] YES / [ ] NO

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* On which platform are the raw data stored?
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3b. Other files

---

* Which other files have been stored?
 - [x] file(s) describing the transition from raw data to reported results. Specify: Data_general discussion
 - [x] file(s) containing processed data. Specify: Processed individual Subjects .eph files (e.g.,pp201.[condition1].eph, pp201.[condition2].eph, pp201.[condition3].eph, pp202.[condition1].eph, pp202.[condition2].eph, etc.), + .xls files of single subject topographical mapping data
 - [x] file(s) containing analyses. Specify: Extracted values from topographical mapping data and imported in SPSS. SPSS files + SPSS output & syntax
 - [ ] files(s) containing information about informed consent
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* On which platform are these other files stored?
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* Who has direct access to these other files (i.e., without intervention of another person)?
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